Prediction related phenomena of visual perception

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Born on the 8th of August 1990 in Leiria, Portugal

Assessors

1. .....

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Day of oral examination: .....

To my grandmother

Summary

Perception is grounded in our ability to optimize predictions about upcoming events. Such predictions depend on both the incoming sensory input and on our previously acquired conceptual knowledge. Correctly predicted or expected sensory stimuli induce reduced responses when compared to incorrectly predicted, surprising inputs. Predictions enable an efficient neuronal encoding so that less energy is invested to interpret redundant sensory stimuli. Several different neuronal phenomena are the consequences of predictions, such as repetition suppression (RS) and mismatch negativity (MMN). RS represents the reduced neuronal response to a stimulus upon its repeated presentation. MMN is the electrophysiological response difference between rare and frequent stimuli in an oddball sequence. While both are currently studied extensively, the underlying mechanisms of RS and MMN as well as their relation to predictions remains poorly understood. In the current thesis, four experiments were devised to investigate prediction related phenomena dependent on the repetition probability of stimuli. Two studies deal with the RS phenomenon, while the other two investigate the MMN response. In Experiment 1 the temporal dynamics underlying prediction and RS effects were tested. Participants were presented with expected and surprising stimulus pairs with two different inter-stimulus intervals (0.5s for Immediate and 1.75 or 3.75s for Delayed target presentation). These pairs could either repeat or alternate. Expectations were contingent on face gender and were manipulated with the repetition probability. We found that the prediction effects do not depend on the length of the ISI period, suggesting that Immediate and Delayed cue-target stimulus arrangements create similar expectation effects. In order to elucidate the neuronal mechanisms underlying these prediction effects (i.e. surprise enhancement or expectation suppression), in our second study, we employed the

experimental design of the first experiment with the addition of random events as a control. We found that surprising events elicit stronger Blood Oxygen Level Dependent (BOLD) responses than random events, implying that predictions influence the neuronal responses via surprise enhancement. Similarly, the third experiment was employed to disentangle which neural mechanism underlies the visual MMN (vMMN). We compared the responses to the stimuli (chairs, faces, real and false characters) presented in conventional oddball sequences to the same stimuli in control sequences (Kaliukhovich and Vogels, 2014). We found that the neural mechanisms underlying vMMN are category dependent: the vMMN of faces and chairs was due to RS, while the vMMN response of real and false characters was mainly driven by surprise-related changes. So far, no study used category-specific regions of interest (ROIs) to examine the neuroimaging correlates of the vMMN. Therefore, for the fourth experiment, we recorded electrophysiological and neuroimaging data from the same participants with an oddball paradigm for real and false characters. We found a significant correlation between vMMN (CP1 cluster at 400 ms) and functional magnetic resonance imaging adaptation (in the letter form area for real characters), suggesting their strong relationship. Taking the four studies into consideration, it is clear that surprise has an important role in prediction related phenomena. The role of surprise is discussed in the light of these results and other recent developments reported in the literature. Overall, this thesis suggests the unification of RS and MMN within the framework of predictive coding.

Zusammenfassung

Unsere Wahrnehmung basiert auf der Fähigkeit, Vorhersagen über kommende Ereignisse zu optimieren. Solche Vorhersagen beruhen sowohl auf sensorischem Input als auch auf bereits vorhandenes konzeptuelles Wissen. Korrekte Vorhersagen und erwartete Sinnesreize lösen, im Vergleich zu falschen Vorhersagen oder überraschenden Sinnesreizen, eine geringere Reaktion aus. Vorhersagen erlauben eine effiziente neuronale Kodierung, sodass weniger Energie für die Interpretation redundanter Sinnesreize notwendig ist. Einige neuronale Phänomene resultieren aus diesen Vorhersage-Effekten, wie etwa die Wiederholungsunterdrückung (RS von englisch *repetition suppression*) und die *Mismatch*-Negativität (MMN). RS ist die verminderte Reaktion auf wiederholte Reize. MMN ist der Unterschied in der elektrophysiologischen Reaktion zwischen selten und häufig präsentierten Reizen in einer *Oddball*-Abfolge. Beide Phänomene sind Gegenstand vieler aktueller Untersuchungen, aber dennoch sind die tiefer liegenden Mechanismen von RS und MMN, sowie deren Bezug zu Vorhersagen, nach wie vor nur mangelhaft erklärt. In der vorliegenden Dissertation werden vier Experimente vorgestellt, die vorhersagenbezogene Phänomene in Abhängigkeit von der Wiederholungswahrscheinlichkeit der Reize untersuchen. Zwei Experimente untersuchen das RS Phänomen, während die anderen beiden Experimente die MMN-Reaktion untersuchen. In Experiment 1 wird die zeitliche Dynamik von Vorhersagen und RS-Effekten untersucht. Den Teilnehmern wurden erwartete und unerwartete Reizpaare mit zwei verschiedenen Inter-Stimulus-Intervallen (ISI; 0,5 s für sofortige und 1,75 s beziehungsweise 3,75 s für verzögerte Präsentation des zweiten Stimulus) gezeigt. Die Paare konnten sich wiederholen oder abwechseln. Die Erwartung wurde durch das Geschlecht der präsentierten Gesichter bedingt und diese wurde durch die

Wiederholungswahrscheinlichkeit manipuliert. Wir fanden heraus, dass sich die Dauer des ISI nicht auf die Vorhersage-Effekte auswirkt. Die Präsentation des zweiten Stimulus sofort nach dem ersten Reiz erzeugte einen ähnlichen Erwartungseffekt wie die verzögerte Präsentation. Um die neuronalen Mechanismen dieser Vorhersage-Effekte (also die Verstärkung bei Überraschung, beziehungsweise die Unterdrückung bei erfüllter Erwartung) zu untersuchen, haben wir in unserem zweiten Experiment den Versuchsaufbau des ersten Experiments herangezogen und zufällige Ereignisse als Kontrollbedingung hinzugefügt. Wir fanden heraus, dass überraschende im Vergleich zu zufälligen Ereignissen eine stärkere BOLD-Reaktion (BOLD steht für *blood oxygen level dependent*) auslösten. Das weist darauf hin, dass Vorhersagen die neuronale Reaktion mittels Überraschungsverstärkung beeinflussen. Daran anlehnend wurde in Experiment 3 untersucht, welche neuronalen Mechanismen der visuellen MMN (vMMN) zugrunde liegen. Wir haben die Reaktion auf Stimuli (Stühle und Gesichter, sowie echte und erfundene Schriftzeichen) in einer *Oddball*-Reizabfolge mit der Reaktion auf dieselben Stimuli in einer Kontrollanordnung verglichen (Kaliukhovich und Vogels, 2014). Dabei stellten wir fest, dass die zugrundeliegenden Mechanismen von vMMN von der Stimulus-Kategorie abhängig sind: Die gefundene vMMN für Gesichter und Stühle basierte auf RS, während die gefundene vMMN-Reaktion gegenüber echten und erfundenen Schriftzeichen vor allem auf Überraschungseffekten basierte. Bisher gab es noch keine Studie, die kategoriespezifische Regionen verwendet hat, um die *Neuroimaging*-Korrelate von vMMN zu untersuchen. Aus diesem Grund haben wir in unserem vierten Experiment sowohl elektrophysiologische als auch *Neuroimaging*-Daten derselben Teilnehmer aufgenommen, während echte und erfundene Schriftzeichen in einer *Oddball*-Abfolge präsentiert wurden. Wir fanden eine signifikante Korrelation zwischen der gefundenen vMMN (im Bereich der Elektrode CP1 bei 400 ms) und des Adaptationseffekts bei der funktionellen

Magnetresonanztomografie (in der Region der Buchstabenverarbeitung für echte Schriftzeichen). Diese Korrelation deutet auf einen engen Zusammenhang von vMMN und Adaptation. Unter Berücksichtigung dieser vier Studien wird klar, dass Überraschung eine wichtige Rolle bei vorhersagenbezogenen Phänomenen spielt. Die Rolle von Überraschungseffekten wird anhand dieser Ergebnisse und mit Hinblick auf neue Entwicklungen in der wissenschaftlichen Literatur diskutiert. Insgesamt schlägt diese Dissertation eine Vereinigung von RS und MMN innerhalb des *Predictive-Coding*-Modells vor.

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Abbreviations

AB	Alternation Block
Alt	Alternation Trial
aMMN	Auditory Mismatch Negativity
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependent
Dev	Deviant
EEG	Electroencephalography
EPI	Echo-Planar Imaging
ERP	Event Related Potential
ES	Expectation Suppression
FFA	Face Fusiform Area
fMRI	Functional Magnetic Ressonance
fMRIa	Functional Magnetic Ressonance Adaptation
GLM	General Linear Model
HRF	Hemodynamic Response Function
ISI	Inter Stimulus Interval
IT	Inferior Temporal Cortex
ITI	Inter Trial Interval
LFA	Letter Form Area
LO	Lateral Occipital Cortex
LOC	Lateral Occipital Complex
MEG	Magnetoencephalography
MMN	Mismatch negativity
MP-RAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic Ressonance Imaging
OFA	Occipital Face Area

PC	Predictive Coding
PE	Predictive Error
pFs	Posterior Fusiform Subregion
Prep	Probability of Repetition
pSTS	Posterior Superior Temporal Sulcus
RB	Repetition Block
Rep	Repetition Trials
ROI	Region of Interest
RS	Repetition Suppression
RSI	Repetition Suppression Index
SSA	Stimulus Spefic Adaptation
Stand	Standard
STS	Superior Temporal Sulcus
T_1	Longitudinal Relaxation Time
T_2^*	Transverse Relaxation Time
TE	Time to Echo
TMS	Trans-cranial Magnetic Stimulation
TR	Time to Repetition
vMMN	Visual Mismatch Negativity
WFA	Word Form Area

'Just like words fail when they try to express any thought,

thought fails when it attempts to express any reality'

Fernando Pessoa

I Introduction

The brain is constantly exposed to abundant sensory information that must be efficiently processed to induce appropriate reactions. This processing effort can be optimized by predicting the incoming sensory information based on previous experience. Such optimization is necessary not only because the sensory information is abundant, but also because it is continuous, ambiguous and incomplete. For this reason, prior knowledge about the regularities of the environment is necessary to reduce the computational complexity of the processes related to perception. In terms of the brain, neuronal processes act on the incoming information in a way that resources can be reserved to novel or surprising information. One important model describing the neuronal processing optimization is Predictive Coding (Rao and Ballard, 1999). Predictive Coding theories state that the brain continually generates models of the world based on context and information from memory to predict sensory input. The present thesis focuses on the neuronal mechanisms related to predictive coding.

This thesis concentrates in predictive processes associated with visual information (with focus on objects, characters and faces) since vision often dominates over the other perceptual modalities (Stokes and Biggs, 2014). Therefore, Subchapter 1 of the Introduction includes a description of the ventral visual stream and its sub visual areas responsible for the shape recognition.

In Subchapter 2, a general review about the basic neuronal phenomena (repetition suppression and mismatch negativity) that signal the influence of the statistical regularities in the environment in terms of temporal contextual factors is laid out. These phenomena are consequences of sensory predictions.

The Predictive Coding framework is described in detail in Subchapter 3. This includes theoretical and computational backgrounds, the current model and how can these theories explain the basic phenomena described in the Subchapter 2.

The Subchapter 4, closing the Introduction section, presents the questions and hypothesis behind the four experiments included on the current thesis.

1 The ventral visual stream

The primary visual cortex transfers information to higher visual areas, which are separated into two independent, but interconnected processing pathways, referred to as the ventral and the dorsal visual streams. Those streams are also known as the 'what' and 'where' pathways, respectively. The current thesis relates with the ventral visual stream, the 'what' pathway. This stream is located in the occipital and temporal cortex (Fig. I 1), anatomically it contains the inferior occipital, the fusiform and the lingual gyri. The ventral visual stream has an elaborated functional organization. In this subchpater, the representation of shape in the ventral visual system is reviewed.

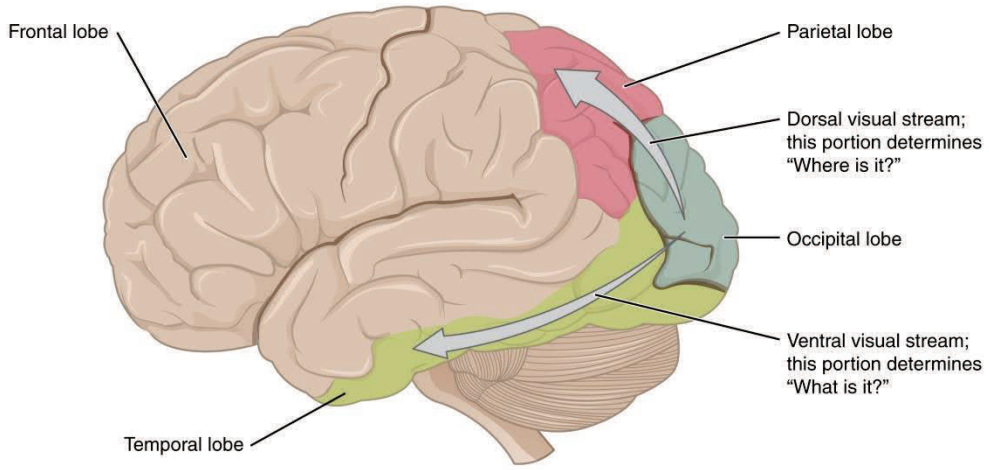

Figure I 1 – Schematic of the ventral and dorsal visual streams. The visual processes start in the occipital lobe, more specifically in the primary visual cortex, which then continue to higher areas, the two visual streams: dorsal and ventral, located in the parietal and temporal lobes, respectively. From Purves et al., (2001)

'Vision is the touch of the spirit'

Fernando Pessoa

1.1 Shape in the ventral visual system

The brain extracts the representation of the shape of a novel visual object within a few hundred milliseconds. The visual system uses different cues to identify, distinguish and evaluate objects based on their shapes, which can range from simple (characters) to extremely complex (faces). The ventral pathway transforms the object shape information into more stable and explicit representations of object shape (i.e. category-selective regions). Its architecture is divided in regions that are selective for certain categories of visual information (Aguirre et al., 1998; Chao et al., 1999; Epstein et al., 2008; Hasson et al., 2003; Haxby et al., 1999; Ishai et al., 1999; Kanwisher et al., 1997a; McCarthy et al., 1997; Puce et al., 1996, 1998). In other words, this stream includes category-related regions, which show response preferences to certain types of stimulus groups (i.e. faces, objects, scenes, characters, bodies etc.). The functional architecture of the ventral visual pathway was observed with neuroimaging techniques, more specifically functional Magnetic Resonance Imaging (fMRI), by comparing the activation of a specific category against others. fMRI enables the measurement of the 'blood oxygenation level dependent' (BOLD) responses of different categories. The comparison of two or more BOLD responses (in what is usually referred to as *contrast)* can be evaluated using statistical parametrical maps. These activation maps indicate which subregions show the peak response for a given category. Researchers concluded that these selective subregions embody the representation of that same category and its perceptual processes.

In this subchapter, the functional neuroanatomy of object, character and face recognition is described and emphasis is given to its related neuronal processes. Other category-selective regions, such as the fusiform body area (Peelen and Downing, 2005), the extrastiate body area (Downing et al., 2001), the parahipocampal place area

(Epstein and Kanwisher, 1998) and the music reading area (Nakada et al., 1998) are not discussed in this subchapter.

1.1.1 Object-selective areas

The lateral occipital complex (LOC; Grill-Spector et al., 1998a; Kanwisher et al., 1997b; Malach et al., 1995; see Fig. I 2) is part of the object-processing network. This complex is usually divided in at least two subregions: the lateral occipital cortex (also known as lateral occipital sulcus, LO) and the posterior fusiform subregion (pFs). The LO is located in the lateral and ventral region of the occipital lobe and the posterior fusiform subregion belongs to the fusiform gyrus. This subsection focuses on the LO, as its responses are tuned to the physical shape of the stimulus and consistent across participants, while pFs responses depend on the observer-specific shape experience and are, therefore, inconsistent across participants (Haushofer et al., 2008).

LO is known to be selective to all visual objects (for review see Grill-Spector, 2003; Grill-Spector et al., 2001), including faces (Lerner et al., 2001; Nagy et al., 2012; Puce et al., 1995). Larsson and Heeger (2006) investigated whether there is a subregion of LO with higher face selectivity. In this study, the LO was divided into two regions (a posterior/dorsal and an anterior/ventral region) and both subregions produced larger responses to objects in comparison with faces. Additionally, LO responses are stronger to stimuli depicting shapes than to low-level features (i.e. colour, motion and texture; see Kanwisher et al., 1997b; Malach et al., 1995). Interestingly, LO responds similarly for familiar ad unfamiliar shapes (Kanwisher et al., 1997b; Malach et al., 1995) and its activation is linearly correlated with performance in object recognition tasks (Ales et al., 2013; Bar et al., 2001; Grill-Spector et al., 2000). Furthermore, LO activation is induced not only by object shape, but also by object position (Cichy et al., 2011, 2013; MacEvoy, 2013; MacEvoy and Yang, 2012; Sayres and Grill-Spector, 2008).

Neurological reports support the notion that the LO is necessary for object recognition (Bridge et al., 2013; Cavina-Pratesi et al., 2010). For example, it was found

than an LO lesion was causing a patient to suffer from a profound loss of visual perception, i.e. visual agnosia (James et al., 2003). Furthermore, transcranial magnetic stimulation (TMS; Walsh and Cowey, 2000) on LO constitutes further evidence that the LO is necessary for object perception (Mullin and Steeves, 2011; Stewart et al., 2001). TMS enables to investigate the role of selective neural responses by inducing momentaneous impairment in a given region. Importantly, TMS to the LO disrupts the processing of object recognition (Mullin and Steeves, 2011).

1.1.2 Character-selective areas

In the fusiform gyrus, there are two functional regions that respond strongly and selectively to characters and words: the Letter Form Area (LFA; Thesen et al., 2012; see Fig. I 2) and the visual Word Form Area (WFA; Cohen et al., 2000, 2002; Dehaene et al., 2002). Anatomically, these regions are interleaved with the fusiform face area (see I 1.1.3.; Matsuo et al., 2015), in a way that LFA is more posterior than WFA (Thesen et al., 2012; Vinckier et al., 2007). Therefore, the character-selective areas have a gradient of low-to-high level processes in a posterior-to-anterior arrangement.

The commonly used *contrasts* to identify character-selective areas are the following: 1. words vs strings (Cohen et al., 2002); 2. known-characters vs false (Thesen et al., 2012) or known- vs unkown characters (Wong et al., 2009), when testing for WFA and LFA, respectively. Face responsive regions are usually found in both hemispheres, while the character-selective areas only show neuronal activation on the left hemisphere. Interestingly, the "neuronal recycling hypothesis" states that the text-selective areas occupied the existing 'territory' for the face responsive areas (Dehaene and Cohen, 2007, 2011), which induced the lateralization of the text responsive areas to the left hemisphere and a lateralization of the face-selective areas to the right hemisphere (Bouhali et al., 2014). Indeed, the lateralization of language related stimuli to the left hemisphere is a well-known fact (Knecht et al., 2000).

Lesions in character-selective areas can induce pure alexia (i.e. deficit of word reading without impairment of writing and auditory word comprehension), which suggests that LFA and WFA are the key areas for tasks that involve reading (Beversdorf et al., 1997; Damasio and Damasio, 1983; Gaillard et al., 2006; Leff et al., 2001; Sakurai et al., 2006; Starrfelt et al., 2009; for a review see Dehaene and Cohen, 2011).

Please note that of these two character-selective areas, this thesis focuses on the LFA, since one of the chosen stimulus categories is characters. This choice is due to the fact that this region encodes low-level stimuli, i.e. characters, while the WFA encodes words, which are much more complex stimuli in comparison. Additionally, the usage of words as stimuli implies an effect of meaning and therefore demands high-level predictions (Price and Devlin, 2011; Twomey et al., 2011).

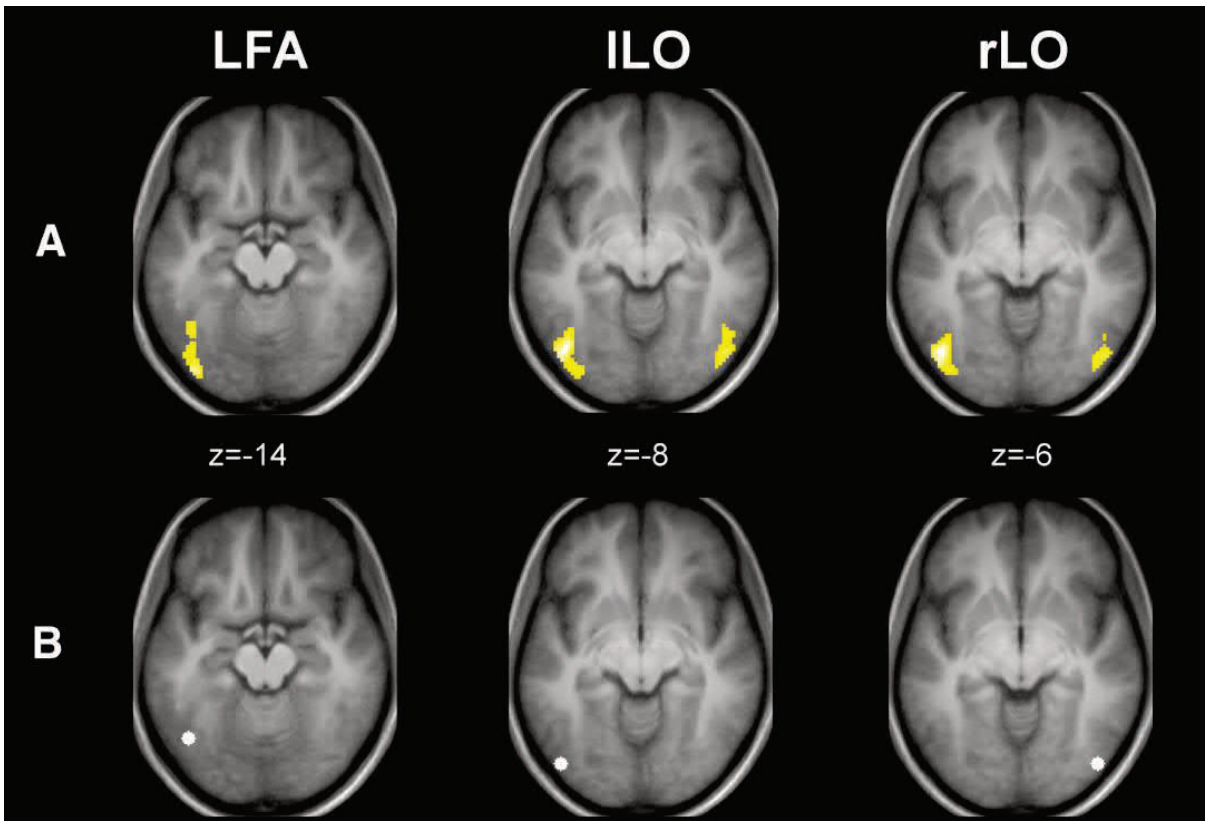

Figure I 2–Character and object selective areas. A. Average activation of the LFA (left column), left LO (middle column) and right LO (right column) of 17 participants. B. A 4mm sphere around the average coordinate peak for the LFA, left and right LO. Please note that in this case the *contrasts* used were the following: 1. real characters vs false characters and Fourier noise images to determine the LFA; 2. real characters vs Fourier noise images to identify the LO. From Grotheer and Kovács (2014).

1.1.3 Face perception network

Given to distinctive evolutionary and social significance of faces, the most developed perceptual skill in humans is probably face perception. Multiple nodes of a distributed network are necessary for face recognition (Fairhall and Ishai, 2007; Ishai, 2008; Van Belle et al., 2011).

There is a growing consensus that the face-perception network is divided into a 'core' and an 'extended' system (Haist et al., 2013; Haxby et al., 2000; Ishai, 2008; Ishai et al., 2005; Van Belle et al., 2011). The core network is responsible for the invariant aspects of faces, such as facial features and identity (Haxby et al., 2000). The core regions include the fusiform face area (FFA) in the middle fusiform gyrus (Kanwisher et al., 1997a; McCarthy et al., 1997; Sergent et al., 1992), the occipital face area (OFA; Gauthier et al., 2000) in the lateral inferior occipital gyrus, the lateral occipital sulcus (LOS, described above in the section I 1.1.1.), and the posterior superior temporal sulcus (pSTS) (Gobbini and Haxby, 2007; Rossion et al., 2003).

It is important to note that regardless of specific task demands, the mature core system (particularly the FFA and OFA) is always activated when viewing faces. Activation of these regions has been shown with the following tasks: remembering/matching specific faces (Epstein et al., 2006; Gauthier et al., 2000b; Mazard et al., 2006; Xu, 2005a; Yovel and Kanwisher, 2004a, 2005), passive viewing (Grill-Spector et al., 2004; Haist et al., 2010; Kanwisher et al., 1997a; Rhodes et al., 2004; Wojciulik et al., 1998) and implicit presentation (Cantlon et al., 2011; Kouider et al., 2009; Morris et al., 2007). However, the activation of the pSTS depends on dynamic feature processing tasks, such as monitoring eye gaze and mouth movements (Hoffman and Haxby, 2000; Puce et al., 1999).

On the other hand, the extended system tends to be task specific (Fairhall and Ishai, 2007; Gobbini and Haxby, 2007; Haxby et al., 2000; Ishai et al., 2005). For example, the anterior temporal lobe (also known as anterior cingulate Kaplan et al., 2007; Redcay et al., 2010) mediates aspects of identity, name, and biographical information (Kriegeskorte et al., 2007; Nestor et al., 2011; Simmons and Martin, 2009) and is activated on tasks related to individuation of faces and biographical information retrieval tasks (Gobbini and Haxby, 2007; Kriegeskorte et al., 2007; Nestor et al., 2008, 2011). Also, the amygdala, which processes the emotional aspects of face representations (Fairhall and Ishai, 2007; Gobbini and Haxby, 2007; Haxby et al., 2000) and is therefore activated on when such analysis is required (Bzdok et al., 2011; Gobbini and Haxby, 2007; Ishai et al., 2004; Schulz et al., 2009).

When the face processing task goes beyond the general appearance of a face, other regions are recruited. Note that not only the amygdala and the anterior face lobe belong to the extended system; all extra regions necessary for the task of processing faces are considered parts of the extended network, like the insula region in the limbic system. Tasks involving recollection of semantic knowledge for faces may engage the inferior frontal gyrus, whereas episodic memory retrieval may recruit the precuneus, posterior cingulate cortex, and medial temporal lobe (Gobbini and Haxby, 2007; Leveroni et al., 2000).

It is important to state that the prediction related phenomena investigated in this thesis are not complex enough to require the involvement of the extended system regions. Therefore, in this subsection only the core system areas (FFA, OFA and pSTS) are described.

i. Face Fusiform Area

Early research revealed that a certain region of the fusiform gyrus was extremely selective to faces (Kanwisher et al., 1997a; McCarthy et al., 1997; Puce et al., 1996 for a review see Kanwisher and Yovel, 2006; see Fig. I 3). This region was named the face fusiform area (FFA) and could be detected with a functional localizer *contrast* of faces vs objects (faces > objects; for an extensive comparison between face and several object responses in FFA see Grill-Spector et al., 2004 and Spiridon and Kanwisher, 2002). Anatomically, this region is located above the cerebellum on the ventral surface of the occipito-temporal cortex. Given the improvement of the existing neuroimaging techniques, two subsections of FFA have been found: a posterior and an anterior subregion (pFus and mFus, respectively; Grill-Spector and Weiner, 2014; Weiner and Grill-Spector, 2010, 2013).

Interestingly, Puce et al., (1996) reported on how texture stimuli can also activate regions within the occipitotemporal and inferior occipital sulci, where the face fusiform area is located. Therefore, other *contrasts* are currently being used for the detection of the FFA, such as faces vs objects and *Fourier* randomized versions of faces (see Grotheer and Kovács, 2015). The usage of two categories of stimulus to *contrast* with face stimuli serves to ensure that the active voxels are not involved in processing objects nor the Fourier randomized faces, i.e. textures (Kanwisher et al., 1997a; Puce et al., 1996).

Furthermore, FFA responds to frontal and profile images of faces, as well as to cats and cartoon faces (Tong et al., 2000). Interestingly, this region is activated by face imagery task (O'Craven and Kanwisher, 2000) and its response to faces is about twice as large when compared to other types of visual input (Kanwisher, 2010). FFA is also known to respond less to inverted than to up-right faces (Yovel and Kanwisher, 2005), which is connected with configural/holistic face processes steps (Rossion, 2008;

Rossion and Gauthier, 2002; but see Yovel and Kanwisher, 2004 for another conclusion) and, therefore, with the recognition faces (Cabeza and Kato, 2000). Indeed, some research reveals that FFA plays an important role regarding face recognition (Gauthier et al., 2000b; Tanaka and Gauthier, 1997). The neuronal activation to the presentation of correctly identified faces was higher when compared to unidentified or unfamiliar faces (Grill-Spector et al., 2004). Another study reported increased FFA activations for faces made familiar through a training procedure (Eger et al., 2005; Pourtois et al., 2005; Verosky et al., 2013). However, some studies reveal no differences regarding familiarity levels of face processing in the FFA (Gorno-Tempini and Price, 2001; Gorno-Tempini et al., 1998)(Barton et al., 2002). Therefore, the subject is still under debate.

Additionally, certain neurological disorders can lead to abnormalities in face perception, which are connected to the impairments of the anatomical and functional characteristics of the FFA. For example, prosopagnosic individuals have lesions in this area (Barton et al., 2002) due to low grey-matter volume in the fusiform gyrus (Garrido et al., 2009a), which leads to diminished face selectivity characteristics of FFA and, therefore, to the inability to identify faces (Furl et al., 2010). Other lesions in the fusifom gyrus can generate poor abilities in tasks involving face individuation (Wada and Yamamoto, 2001) and detection (Xu et al., 2014). Autism spectrum disorder might also lead to atypical selectivity and connectivity in the FFA (Khan et al., 2013; Nickl-Jockschat et al., 2015; Vuontela et al., 2013). Moreover, it is possible to 'knock-out' the FFA by using electrical brain simulation techniques (EBS). Similarly to TMS, this technique induces a momentary impairment in the functioning of a region of interest (ROI) to directly investigate the causal role of selective neural responses, in this case face-selective. When the FFA is 'knocked-out', face perception is distorted, but word or object perception remains intact (Parvizi et al., 2012; Rangarajan et al., 2014). These

studies constitute important evidence of how the FFA plays a crucial role regarding face perception mechanisms. In fact, this region is usually described as a key site for face selective processes, such as the holistic and configural steps (Maurer et al., 2007; Mazard et al., 2006; Rhodes et al., 2009; Yovel and Kanwisher, 2004b).

However, other studies defend that the FFA is not only involved in processes of face perception but for general stimuli requiring high expertise, i.e. stimulus categories to which participants have had great experience with when compared with other objects. Indeed, evidence of such response selectivity for stimulus of high-expertise has been found for FFA (Bilalić et al., 2011; Gauthier et al., 1999, 2000c; James and James, 2013; Xu, 2005b). Even if these findings are under debate, the role of FFA in face perception is undisputed (for further discussion see Bukach et al., 2006; Harel et al., 2013; Kanwisher and Yovel, 2006; McKone et al., 2007).

ii. Occipital Face Area and Superior Temporal Sulcus

Later on, another face-selective region was found and called occipital face area (OFA; Davies-Thompson and Andrews, 2012; Gauthier et al., 2000b; Zhu et al., 2011). This region, as the FFA, is part of the face perception network and is located on the lateral surface of the occipital lobe near the inferior occipital gyrus (see Fig. I 3). In this network, the OFA has a core role as it receives the visual information first and then communicates with the FFA via cortical routes (Calder and Young, 2005; Haxby et al., 2000; Ishai, 2008; Pitcher et al., 2011).

The OFA performs the first face computations, by separately encoding the facial components (nose, mouth, eyes; see Liu et al., 2010; Nichols et al., 2010), which are considered to make it more sensitive to physical components of face processing than the FFA (Rotshtein et al., 2005). These computations are done relatively fast, in around 100ms post-stimulus onset (Pitcher et al., 2007; Sadeh et al., 2010). The OFA is therefore considered as the first stage of the face perception in the model created by Bruce and Young, (1986), where the face preprocessing of the structural encoding takes place (Pitcher et al., 2011). However, a recent TMS study shows that the OFA is not limited to the processing of low-level physical features and has an important role in the encoding of face identity and in the creation of identity-specific memory traces (Ambrus et al., 2017).

Furthermore, certain prosopagnosic patients have no damage in the FFA, in their case the neuronal abnormalities in the OFA region are the cause of the inability to identify faces (Rossion et al., 2003; Steeves et al., 2006). These findings constitute clear evidence of the importance of the OFA in face perception, suggesting that the FFA is connected to the OFA and/or the independent processes on the OFA and the FFA. Other studies used TMS in healthy participants to test the role of the OFA in face recognition and categorization (see Solomon-Harris et al., 2013). These studies reveal

that the OFA is crucial for face recognition, but not for face categorization (for a review see Atkinson and Adolphs, 2011), bringing into question the OFA's specificity to process low-level information (Rossion and Jacques, 2008; Solomon-Harris et al., 2013). Indeed, other studies confirm that not only the OFA, but also the FFA is responsive to low-level information (Andrews et al., 2010; Yue et al., 2011).

Superior temporal sulcus (STS; Perrett et al., 1982) is another region from this face-processing network (Kanwisher et al., 1997a). The STS is located in the temporal lobe between the superior temporal gyrus and the middle temporal gyrus. This region responds to facial movement and expressions (Hasselmo et al., 1989; Haxby et al., 1999; Puce et al., 1998). The STS was first discovered in macaque monkeys by single-cell recording research (Perrett et al., 1985; for more information about single-cell recording technique see the section I 2.1.1.). This work revealed that the STS is responsive to faces (mostly dependent on the viewpoint) and is especially sensitive to gaze direction and contact (see also Andrews and Ewbank, 2004; Calder et al., 2007). Later research on macaques shows that this region is interconnected with facial expression (Hasselmo et al., 1989). In humans, this region is not so commonly detected in both hemispheres (Haxby et al., 1999), although a posterior region of the STS is known to be specific for face recognition with a right hemisphere lateralization (Henson et al., 2003).

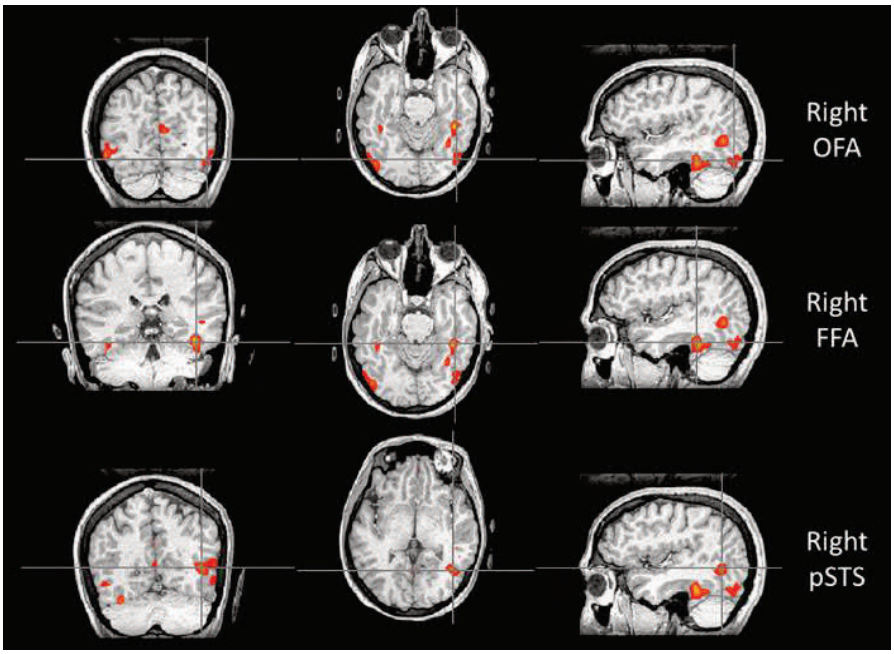

Figure I 3 - Statistical parametrical maps of the face-processing network (from Pitcher et al., 2011) for the following ROIs: right FFA (middle row), OFA (top row) and pSTS (bottom row) in the coronal (left column), axial (middle column) and sagittal (right column) views. The gray lines represent the centre peak of the ROIs.

Please note that of the core network face areas, this thesis focus on the FFA. When compared with the OFA, this region is task independent and also contributes to late stages of face analysis. In other words, the FFA integrates the low-level attributes of a face into a more complex representation (Arcurio et al., 2012; Schiltz et al., 2010). Therefore, the FFA is towards the higher end of the face processing network areas. Also, the FFA is the most studied and well-known area of the ventral visual stream (Kanwisher, 2017).

2 Neuronal-phenomena signalling the influence of temporal context on perception

Our perception is modulated by prior experiences in terms of temporal and spatial context, with both temporal and spatial contexts influencing sensory predictions. However, this thesis focuses exclusively on the basic perceptual phenomena influenced directly by the temporal context (see subchapter 3 of the General Discussion for more information about spatial context).

The temporal context can be defined as the fluctuation of regularity within a system or environment in the time dimension. It is of note that the functional properties of the central nervous system signal the temporal fluctuations, i.e. the temporal context. In other words, these neuronal properties have representations of the statistical regularities in the environment and, when necessary, adapt to environmental changes.

Two neuronal phenomena signal the modulations imposed by the temporal context and, as this context serves to create sensory predictions, these phenomena are seen as consequences of predictive processes. This section will include a summary of these two neuronal-phenomena: the repetition suppression (2.1) and the mismatch negativity (2.2).

"Man adapts to everything, every state. There is no life in which time and repetition do not make the acts more natural. "

Almeida Garret

2.1 Repetition Suppression

The effect of stimulus repetition on neural responses is a commonly studied phenomenon in neuroscience. This effect usually manifests in the reduction of the neuronal reponse for repeated when compared to non-repeated stimuli. In other words, repeated stimuli lead to smaller neural activity amplitudes than responses to novel stimuli. The repetition related phenomena are commonly referred to as repetition suppression (RS; for review see Grill-Spector et al., 2006).

In this subsection (2.1), the story, evolution and findings of repetition suppression are reviewed with a special focus on the visual domain. This section is subdivided into the main methodological approaches to investigate repetition related phenomena (single-cell evidence and history, electrophysiological studies and fMRI adaptation).

2.1.1 Single-cell evidence and history

One of the oldest and most popular techniques to measure neural activity is the single-cell electrical recording (Fries et al., 1977; Hubel and Wiesel, 1977). This method allows the measurement of electrical signals in specific cell units. The first studies reporting the existence of repetition related phenomena used single-cell recordings on macaque monkeys (Gross et al., 1979; Li et al., 1993; Miller and Desimone, 1994; Miller et al., 1991; Sobotka and Ringo, 1994; for a initial review see Desimone, 1996). Behaviourally, these experiments relied on one of the following tasks: either delayed matching or recognition tasks. The first one consists of detecting which of the presented stimuli are equal to the very first stimulus in the experiment. The matching sample (i.e. the repetition of the first stimulus) could be presented after 3 or 35 trials. In the case of recognition tasks, the identification of novel stimuli in the experiment was necessary. The animals were trained to perform such tasks and rewarded with juice when successfully accomplished the goal.

These pioneering studies found the phenomenon of repetition suppression, meaning that the maximum response amplitude was registered for the first presentation of a stimulus and subsequent repetitions of the same stimulus induced a decrease on the response amplitude. Note that the cells of interest were chosen *a priori* in areas known to be responsive to the given visual stimulus. In this case, the stimuli were complex objects, which activate the inferior temporal cortex (IT; Gross et al., 1972) of monkeys. The term to describe repetition related phenomena was not consistent in these early studies; some called it repetition suppression (RS; Desimone, 1996; Miller and Desimone, 1994) others referred to it as stimulus specific adaptation (Sobotka and Ringo, 1994).

Originally documented as a form of memory, it has been shown that RS does not depend on the capacity to distinguish between the first presentation of a given stimulus and its repetitions. Miller and Desimone (1994) used delayed matching tasks and repeated some of the non-matching stimuli. The results of Miller's study showed repetition suppression effects for both matching and non-matching repeated stimuli (Fig. I 4A). Another study supports the independence of RS and memory using a visual discrimination task: in this case, monkeys had to press a button for every stimulus within the presentation (Sobotka and Ringo, 1994).

However, not all neurons of a given selective area, as IT, show RS. Some of the recorded cells perform differently and exhibit repetition enhancement (Fig. I 4B; see this review Krekelberg et al., 2006; Segaert et al., 2013), i.e. larger neuronal responses for repeated stimuli, the opposite of repetition suppression. The phenomenon of repetition enhancement has been connected with learning processes (Gruber and Müller, 2005; Henson, 2001; Henson et al., 2000).

Single-cell recordings continue to be used in the current research, but the most recent studies employ different paradigms to better understand repetition related phenomena. Briefly, the most commonly used paradigms today are (see Table I1): 1.Oddball paradigms (see the section 2.2 of the Introduction); 2.Block designs (i.e. the same stimulus is presented within a block,); 3.Delayed match-to-sample designs (see above); 4.Within trial-repetition designs (same-different or categorical/parametrical repetition); 5. Across trial repetition designs. Given to high variability regarding the used paradigm and method (Table I 1), incongruences are prone to appear (for a review see Feuerriegel, 2016). Those can be related to several factors: stimulus specific adaptation, memory retrieval, attention, neuronal selectivity, inherited adaptation and stimulus novelty vs familiarity.

Certain studies try to disentangle how the different techniques differ in the measurement of RS (by comparing single-cell recordings vs fMRI, Magnetoencephalography; MEG). The method of single-cell recordings is rarely used in humans due to its invasiveness, being mostly applied to animals (cats, monkeys, rats, etc.) Therefore, the next sections of this subchapter describe other methods, focusing on human research.

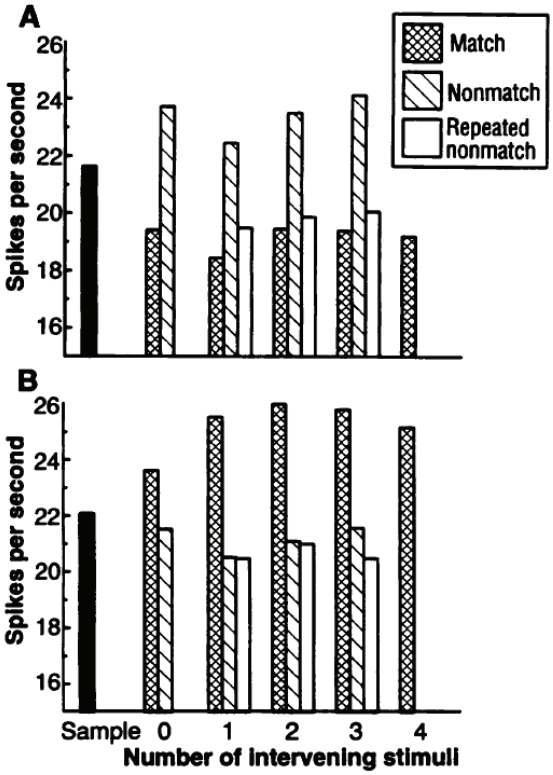

Figure I 4 – Average of the neuronal response in spikes per second for: A. suppression (46 neurons in total) and B. enhancement (total of 45 neurons) mechanisms of repetition in IT. From Miller and Desimone (1994).

Table I 1 – List of the existing paradigms to investigate repetition related phenomena

Paradigm/Designs	Short description
Oddball	Blocks with two stimuli one adaptor (standard) and a deviant, presented with 90% and 10% probabilities, respectively
Block	Within a block (i.e. a longer series of stimulus presentations), the same stimulus is presented repeatedly
Delay to match	A sample stimulus is presented and a matching stimulus appears after a delay of non-matching intervening stimulus
Within repetition *same/different*	Within trial adaptation: RS is measured in comparison to the previous stimulus, only.
Within repetition *categorical/parametrical*	Adaptation to stimulus categories or features
Across trial repetition	Repetition of one single trial separated by long periods

2.1.2 Electrophysiological studies

In humans, the existence of repetition related effects was initially detected as a form of priming – repetition priming, also known as perceptual priming. This phenomenon acts as an improved behavioural response (in terms of reaction time and accuracy) to the stimulus repetition when compared with its first presentation. Priming reflects implicit memory processes (see the following reviews (Schacter et al., 1993; Jacoby and Brooks, 1984; Kristjánsson and Driver, 2008), as it occurs in the absence of awareness of repetition. Certain studies suggest that RS is a neuronal correlate of repetition priming (Bunzeck et al., 2006; Dobbins et al., 2004; Wig et al., 2005; see the section I 2.1.3. for more information on neuroimaging studies). However, there is evidence for dissociation between the two phenomena (Henson and Rugg, 2003; Kaiser et al., 2013; Schacter and Buckner, 1998). In fact, repetition priming and RS have certain similarities: both rely on facilitation mechanisms; the paradigms are identical to those of Table I 1; non-dependent in retrieval; maintainable for different stimulus attributes (Gotts et al., 2012a). Yet, whether RS is a neurophysiological index of repetition priming is still under investigation.

Solid confirmation of RS in humans was found through electroencephalogical experiments (event-related potentials - ERPs and gamma band responses). The first ERP studies revealed an early repetition suppression effect at around 150ms post-stimulus onset (Henson et al., 2004; Schendan and Kutas, 2003). On other hand, data of the gamma band response of ERPs show that frequencies between 53 and 71 Hz only have repetition related effects within a time-window of 260-540ms (Gruber and Müller, 2002). Note that the referred studies focused on repetition priming of complex objects.

Using EEG recordings, others have found repetition priming to face stimuli, for famous, familiar (Fig. I 5; Begleiter et al., 1995; Schweinberger et al., 1995) and

unfamiliar (Hertz et al., 1994) faces. Famous faces show early (180-290ms) and late (>310ms) ERP differences for repeated and novel faces accompanied with enhanced RTs for repetitions (Schweinberger et al., 1995). Unfamiliar faces produce repetition priming effects in the ERPs, although those effects are considerably smaller when compared to repetition priming effects for familiar faces (Schweinberger et al., 2002). Interestingly, facial emotion modulates the extent of repetition suppression, being larger for fearful than for neutral faces (Ishai et al., 2004).

Additionally, recent research indicates that RS effects only appear after 200ms of stimulus onset (Puce et al., 1999; Schweinberger et al., 2004). Also, there is a categorical adaptation (see Table I 1 about this paradigm - within repetition: categorical/parametrical) in form of a reduction of the N170 component[1.] (Harris and Nakayama, 2007; Kloth et al., 2009; Kovács et al., 2006).

The current priming research using characters or words as stimulus relies on semantic instead of repetition priming, i.e. in cases where the prime and the target belong to the same semantic category. Yet, certain EEG studies have found repetition related effects for words and characters repetition (Deacon et al., 2004; Pickering and Schweinberger, 2003; Rugg, 1987; Vidal et al., 2014; Zhang et al., 1997). Notably, differences regarding priming effects were detected for words and non-words.

1. The N170 component depicits an increased negativity around 130-200ms after onset and is usually elicited by face stimuli

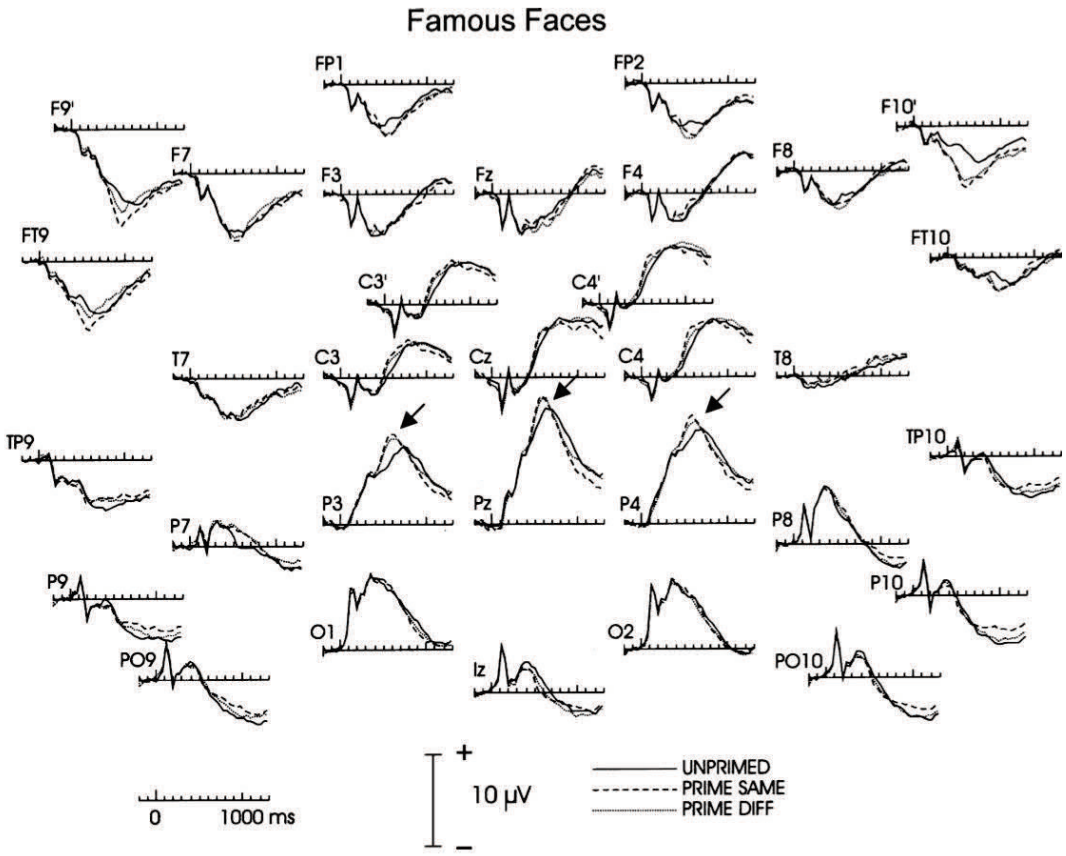

Figure I 5 – ERP recordings of all the 32channels for primed (with the same portrait – repetition priming or with a different portrait of the same identity) and unprimed familiar faces. From Schweinberger et al., (2002).

The technique of EEG enables reasonable understanding of the temporal and the spatial dimensions of repetition related phenomena. However, EEG has a poor spatial resolution to retrace which neuronal regions induced the effects on the electrical signal of the scalp. Other techniques such as MEG and fMRI (see the section I 2.3. for reviews about the fMRI technique see Logothetis, 2002; Logothetis and Wandell, 2004) have a better spatial resolution. MEG is the method with the best tradeoff between space and time measurements, showing good spatial and temporal resolutions. Note that MEG and fMRI measurements can differ, especially for MEG frequencies higher than 100Hz or smaller than 20Hz (Schulz et al., 2004).

While most of the existing MEG research on repetition related phenomena is focused on face stimuli (Deffke et al., 2007; Schweinberger et al., 2007), there is also research on letters, words and objects have also been done (Friese et al., 2012; Pylkkänen and Okano, 2010; Schweinberger et al., 2007). To summarize, these studies show repetition priming effects for within trial repetitions (same/different) of faces in the M250 (i.e. a MEG component that occurs within a time window from 220 till 330ms). Yet, for across trial repetition designs no RS effect was found (Deffke et al., 2007). Furthermore, repetition priming of the M250 was shown to be larger for faces than for objects (Schweinberger et al., 2007).

2.1.3 fMRI adaptation

The functional imaging technique, fMRI when used to investigate repetition related effects is usually referred to as fMRI adaptation (fMRIa, (Grill-Spector and Malach, 2001; James et al., 2002; Vuilleumier et al., 2002; for review see Malach, 2012).

fMRI is an indirect, non-invasive and popular method used to study neuronal activity with a considerably large spatial resolution (for reviews see Logothetis, 2002; Logothetis and Wandell, 2004). Even if there are several thousands of neurons per voxel (the 3D measuring unit of every neuroimaging technique, determining the spatial resolution[2].). Therefore, the fMRI data only captures the net activity of a large neuronal population group (Levy et al., 2004), which can create complicate the analysis of functional selectivity.

Interestingly, this limitation can be surpassed using repetition suppression phenomena. Suppose there is a population of neurons that responds strongly, but selectively to individual viewpoints (this population is, therefore, selective to this property) and another population which responds weakly to all viewpoints (invariant population). In an experiment with similar amounts of stimuli with the same and different viewpoints, conventional fMRI would show similar BOLD responses for both populations, due to the net result.

2. The resolution of micrometer is achieved by the most moder techniques: ultra-high-resolution 7T machines.

In contrast, in fMRIa paradigm, the selective population would show adaptation only if the same viewpoint is repeated, while the invariant population would show a reduced neuronal response to repeating stimulus independently of the viewpoint (i.e. for both viewpoints, different and same). fMRIa is specially tuned to determine the functional properties of a given population and this method has been crucial to understand neuronal selectivity characteristics.

The paradigms used to study fMRIa (Fig. I 6) are similar to the ones described in the Table I 1 (section 2.1.1..; for review on fMRIa paradigms see (Weigelt et al., 2011). Also, as it has been previously referred, different experimental designs most likely target different neuronal adaptation processes. The most important design factors are the repetition lag (variations of the time between the first presentation of a stimulus and its repetition), adaptation duration and number of repetitions (Weigelt et al., 2011). For example, in certain paradigms, the repetition lag is extremely important, especially for the within repetition paradigm (see the section 2.1.1. Table I 1) and in this case the repetition lag is also called inter-stimulus-interval (ISI).

Early research focused on the effects of the ISI length on RS by comparing ISI with short (500ms) and long (1s - 8min) lags. Certain studies reveal no influence of ISI length on RS (Grill-Spector et al., 2006b; Henson et al., 2004), however others suggests that RS effects interact with the repetition lag (Epstein et al., 2008; Kouider at al., 2009; Larsson & Smith, 2012; Weiner et al., 2010).

Interestingly, fMRI studies found an impairment in the repetition related reduction of the BOLD response of certain neurological/psychiatric illnesses such as schizophrenia (Williams et al., 2013), autism (Ewbank et al., 2015), Alzheimer disease (Pihlajamäki et al., 2008, 2011) and prosopagnosia (Williams et al., 2007). These findings emphasize the relevance of RS to understand brain functions.

However, as in the techniques mentioned above, neuronal suppression and enhancement might be integrated within the same BOLD signal and neuronal population. Certain studies used both MEG and EEG to show that repetition effects can shift from repetition enhancement to repetition suppression in a later time window, as well as from repetition suppression to repetition enhancement, even within the same region (Marinkovic et al., 2003; Petit et al., 2006). Repetition effects should not only be explained at the level of a group of neurons, but also at the level of individual neurons. Still, at such fine level the underlying neurophysiologic mechanisms and their interactions are not yet fully understood.

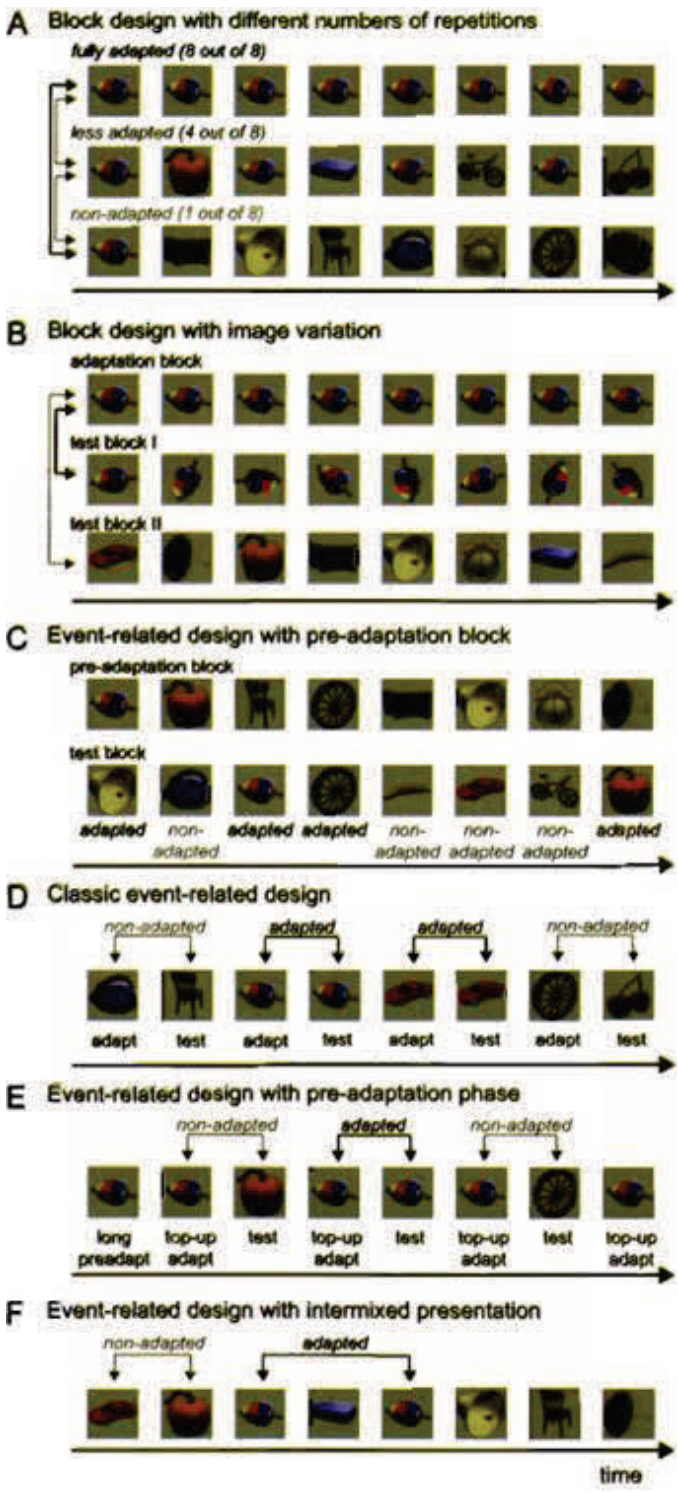

Figure I 6 - Schematic of the different experimental designs that can be used to elicit fMRIa. A. Block design with different numbers of repetitions. In this paradigm different blocks are employed to elicit different adaptation levels (e.g. fully adapted, less adapted and non-adapted). Basically, the reduction of the BOLD signal should vary as a function of the number of repetitions. B. Block design with image variation. Different blocks involve the repeated presentation of a stimulus without (adaptation block) and with (test block I) different variations (e.g. size, position, viewpoint, illumination) which are compared to the non-adapted block (test block II). C. Event-related design with pre-adaptation block. Consists in series of novel object stimuli (pre-adaptation-block) and a series of the same (adapted) objects intermixed with novel objects (non-adapted) in a test-block. D. Classic event-related design. A trial consists of two consecutive stimuli. The adaptor image is always tested immediately. E. Event-related design with pre-adaptation phase. Similar to the Classic event-related design (D), with a long pre-adaptation phase. Following the pre-adaptation phase, there is a classic even-related design in which the same stimulus as of the pre-adaptation phase shown again (for every trial) followed by the test stimulus. F. Event-related design with intermixed presentation. Some stimuli are repeated and some will only occur once. The repetition delay between the first presentation of the stimulus and its repetition is variable. From Weigelt et al. (2011).

2.2 Mismatch Negativity

The mismatch negativity (MMN) response is usually described as an ERP component, which is automatically elicited (i.e. in the absence of attention) by regularity violation (in other words, events that violate predictions based on prior events) in one version of the above described paradigms, the oddball paradigms. MMN is obtained by subtracting the response to unpredicted, rare stimuli from those to predicted, frequent stimuli.

In this subsection (2.2), both auditory (MMN) and visual mismatch negativity (vMMN) are described as well as the oddball studies employing neuroimaging techniques (specialy fMRI).

2.2.1 Auditory

The MMN phenomenon was first described on the auditory domain (aMMN; Näätänen et al., 1978; for an extensive review see Näätänen et al., 2010) and is elicited by violations in the regular aspects of the auditory stimulation.

The oddball paradigm is commonly used on MMN studies. Basically, the participant is presented with frequent stimuli at short intervals (standard; consisting in 90% of the presentation), which are infrequently (10% of the times) replaced with a deviant stimulus (a stimulus audibly different from the standard; for example a differently pitched tone). When the standard repetitive stimulation is interrupted by a deviant, a MMN response is elicited. Note that the ERPs responses to deviant and standard stimuli are similar, although the deviant-minus-standard-stimulus ERP usually reveals negativity in the 100-200 ms poststimulus latency range (Fig. I 7). This negative ERP component of the MMN is usually generated in the auditory and frontal cortices (see Alho, 1995).

Interestingly, MMN is not dependent on attention, as it can also be elicited when the auditory stimuli are not noticed (in acoustic studies). Therefore, MMN is normally recorded in an “ignore condition”, i.e. when participants are performing a task that is not related to the auditory stimulation (e.g. reading a book or watching a video). The ignore condition enables the recording of pure MMN since there is no contamination of attentive deviance processing in the ERP components (Tervaniemi et al., 1997). However, the amplitude of the MMN effects depends on the ISI, in a way that the MMN effect reduces proportionally to the increase of ISI (see Näätänen et al., 2004; Sams et al., 1993).

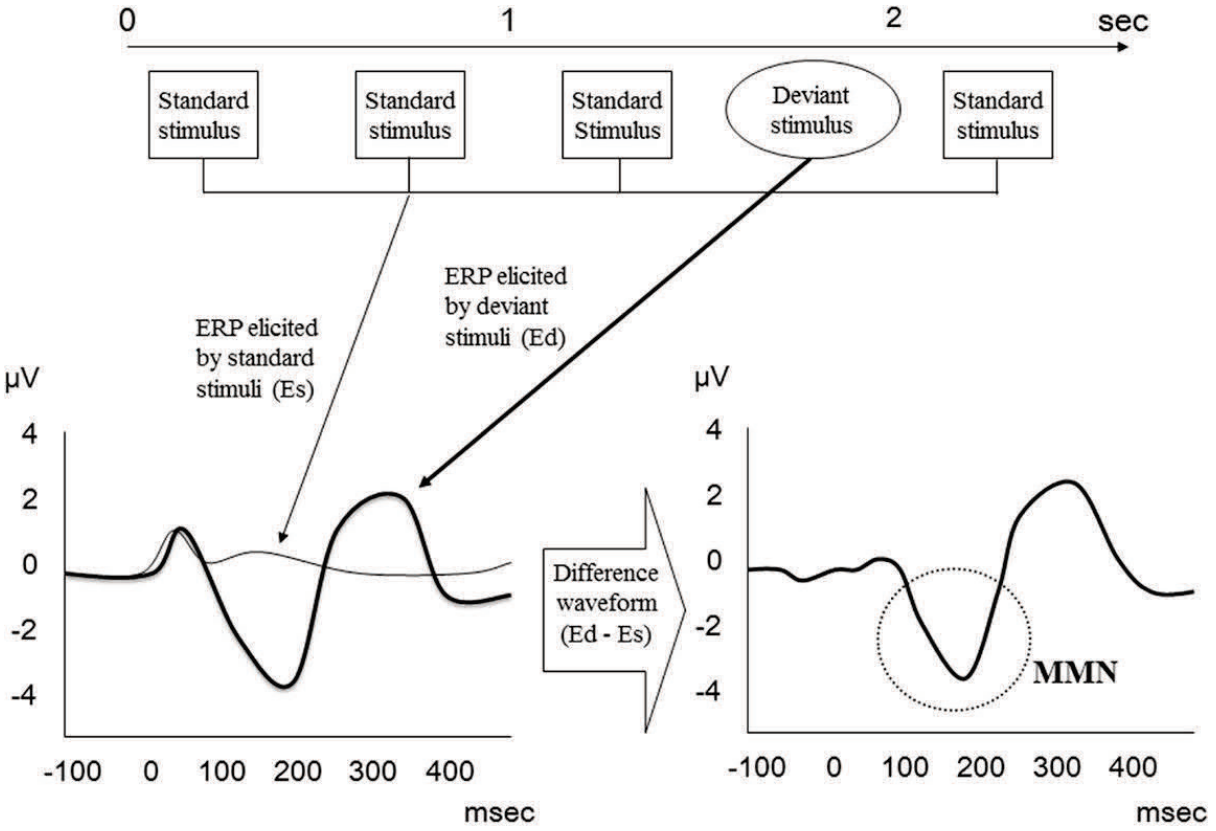

Figure I 7 – Schematic of mismatch negativity. Top: Illustration of a common oddball paradigm. Bottom left: ERPs elicited by standard stimuli (Es; grey) and deviant stimuli (Ed; bold). Bottom right: MMN corresponds to the difference ERP and is obtained by subtracting the standard stimulus ERP from the deviant stimulus ERP. From Nagai et al. (2013).

Early MMN studies interpreted this phenomenon as a pre-attentive, automatic mechanism elicited by a memory system, suggesting that MMN generation relied on a strong auditory sensory memory trace encoding the repeating stimulus (Winkler, 2007). This interpretation is also known as the "surprise" or "genuine" MMN (Stefanics et al., 2014). There was an earlier, alternative explanation for this phenomenon: the adaptation model (May and Tiitinen, 2001; May et al., 1999; for a review see May and Tiitinen, 2010). This model defends that the differences between standard and deviant stimuli is due to an adaptation (also known as refractoriness or stimulus specific

adaptation – 'SSA') of the neuronal population to the standard, leading the population to respond strongly to the deviant.

The majority of studies use simple oddball paradigms in which the standard and deviant stimuli vary in terms of physical, concrete, "first-order" features (e.g. frequency, intensity, spatial location) (Näätänen et al., 1978; Sams et al., 1985). However, MMN can also be elicited by more complex, abstract, "higher-order" regularities or invariances (Saarinen et al., 1992). For example, rules determining the occurrence of specific stimuli in the auditory stream (e.g. a sequence of descending tones) or even relationships between various physical features as speech (Tervaniemi et al., 1997; for a review see Paavilainen, 2013). Figure I 8 depicts the difference between a classic physical oddball paradigm and an abstract-feature paradigm.

Another way to induce MMN relies on changes of the temporal features of the stimulation, such as infrequent stimulus omission (Nordby, 1991; Yabe et al., 1997, 1998), duration of stimulus presentation (Kaukoranta et al., 1989; Näätänen et al., 1989; Paavilainen et al., 1991), or even ISI (Nordby et al., 1988a, 1988b). These findings are usually used as an argument against the adaptation explanation of the MMN (May and Tiitinen, 2010a).

A prerequisite to elicit MMN is that the central nervous system has formed a representation of repetitive aspects (physical or abstract) in the auditory stimulation before the occurrence of the deviant stimulus (Näätänen and Winkler, 1999; Winkler et al., 1996a). There are several processes behind the MMN response, including stimulus anticipation and extrapolation, sequential stimulus-rule extraction and pattern and pitch interval encoding (for a review see Näätänen et al., 2010b). Interestingly, MMN effects have also been found in sleeping newborn babies (Cheour

et al., 2002; Glass et al., 2008), anesthetized animals and deeply sedated adults (Koelsch et al., 2006), indicating that they reflect core perceptual-cognitive processes.

Several animal species have shown MMN-like effects: monkeys (Javitt et al., 1992, 1996), cats (Csépe et al., 1987; Pincze et al., 2001, 2002), rats (Astikainen et al., 2006, 2011), guinea pigs (Kraus et al., 1994), rabbits (Astikainen et al., 2005) and mice (Umbricht et al., 2005). The MMN recorded in different animals seems to be analogous to the one found in humans, at least in terms of the dependence to the inter-stimulus interval as well as the neuronal generators of these signals (for details see Näätänen et al., 2010b). However, some studies failed to find "genuine" MMN responses in the primary auditory cortex (Farley et al., 2010; Fishman and Steinschneider, 2012); yet MMN might be present in higher auditory areas (Szycik et al., 2013).

Furthermore, the amplitude of MMN is attenuated in different severe psychiatric (such as autism and schizophrenia, see Dunn et al., 2008 and Umbricht and Krljes, 2005, respectively) and neurodegenerative diseases (e.g. Alzheirmer's disease; see Pekkonen et al., 1994). Nonetheless, the actual extent of the sensory intelligent processes of automatic nature that is preserved or affected in such diseases is still an open question (Näätänen et al., 2010).

More recent theories interpret MMN as an automatic representational difference elicited by the violation of regularities established in an environment (for more details see the section I 3.4.). These theories, thus, defend that the formation of predictions is the primary function of the neural processes underlying MMN, in a way that the perceptual system extracts environmental regularities and represents expected events. However, the hypothesis that adaptation explains MMN has not been ruled out (May and Tiitinen, 2010b; Symonds et al., 2017).

There is a late mismatch negativity component also referred to as a *late discriminative negativity* (LDN; Cheour et al., 2001; Näätänen et al., 1982). This effect can also be elicited by deviant stimuli in oddball paradigms and usually occurs between 400-700ms post-stimulus onset. The functional significance of LDN is not clear and several explanations have been given to this effect: For example, 1. Higher cognitive processes, such as attention-related processes, letter-speech sound integration, and long-term memory (Neuhoff et al., 2012); 2. Automatic preparation to detect additional stimuli (Mueller et al., 2008; Näätänen et al., 1982); 3. Attentional reorienting back to the original task (Escera et al., 2000; Munka and Berti, 2006; Schröger and Wolff, 1998).

An analogous response occurs in the other sensory modalities too. MMN effects have been found for the following domains: somatosensory (Akatsuka et al., 2005, 2007; Kekoni et al., 1997); olfactory (Krauel et al., 1999; Pause and Krauel, 2000); visual (for reviews, see Kenemans et al., 2003; Stefanics et al., 2014).

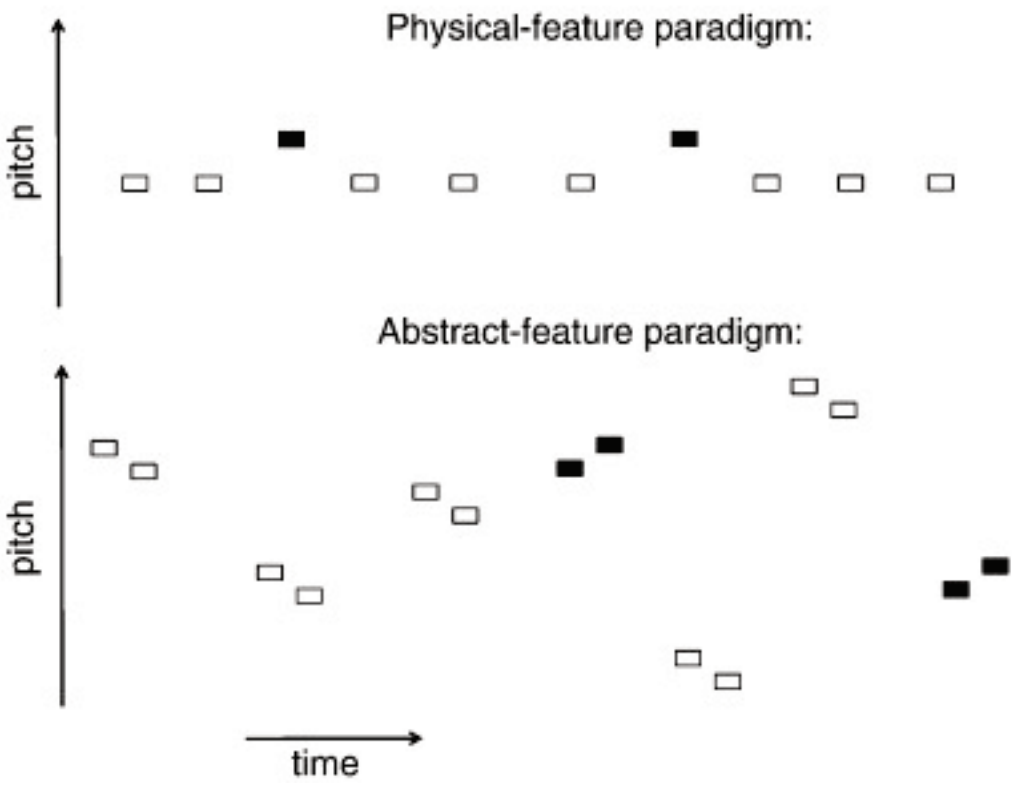

Figure I 8 – Illustration of physical- and abstract-feature paradigms used to elicit MMN: Standard stimuli are represented by the white rectangles, while deviant stimuli are depicted by the black rectangles. For both paradigm types the auditory stimuli are tones that vary in terms of pitch. A. Physical-feature paradigm: in this case the standard is a physically invariant stimulus, which is repeatedly presented. A deviant stimulus (a tone of a higher pitch) is occasionally presented instead of the standard stimulus. B. Abstract-feature paradigm: tone pairs differing in pitch are presented. However, there is a high-order feature defining the standards, which is the direction of the within-pair pitch change: the standard pairs are descending in pitch, while deviant pairs are ascending. Note that the pitch of the pair is randomly varying in a way there is no physical invariant feature. From Paavilainen (2013).

2.2.2 Visual

For years there was controversy about the existence of MMN in the visual modality. This uncertainty was mainly due to: 1. Lack of results' interpretation (Alho et al., 1992; Czigler and Csibra, 1990; Czigler et al., 1992; Woods et al., 1992); 2. Early negative results (Nyman et al., 1990); 3. Lack of phenomenological awareness of visual changes in the absence of attentive processing (for example change blindness; Rensink et al., 1997), 4. Absence of a short-term categorical visual storage (Irwin, 1992; for a review see Czigler, 2007). However, since then substantial evidence has been accumulated for the existence of visual mismatch negativity (vMMN; Stefanics et al., 2014; for an early review see Pazo-Alvarez et al., 2003).

As in the classical auditory MMN domain, the vMMN is induced by the repetition of a stimulus, yet it does not only operate at the level of simple, physical sensory features, but also at higher, abstract cognitive levels. The physical features know to induce vMMN are the following: colour; spatial frequency; brightness; stimulus contrast; motion direction; shape; line orientation; stimulus location; conjunction of colour and direction; stimulus omission and deviant stimulus sequence (for reviews see Czigler, 2007; Stefanics et al., 2014). More recent studies show several types of abstract-feature vMMN, such as object-based irregularities; irregular lexical information; sequential regularities; changes in simple geometric patterns; illusory brightness; changes in attributes of complex natural stimuli (e.g. laterality of body parts); facial emotions and gender.

vMMN studies usually control possible attentional processes with concurrent visual tasks, because in the absence of concurrent visual events it is hard to withdraw attention from visual stimuli. Since vision is considered to be the dominant sensory modality, visual distractors cause more interference to auditory than to visual

processing. Different techniques have been used to ensure the participants' attention is away from the mismatch-evoking stimuli, such as: tracking; deviant in attentional blink position; central task on the sequence of vMMN-related stimuli (independently or dependently); central task with Standard or/and Deviant stimuli of the vMMN related sequence; feature of the task-related stimuli; auditory task; fixation or target-related stimuli (for a review Stefanics et al., 2014).

The interpretation of the vMMN is similar to that of aMMN: it is a reflect of automatic perceptual error responses to events violating statistical regularities, i.e. the "surprise" response (genuine vMMN), but it can also be interpreted as short term synaptic plasticity involving SSA. It is possible to to disentangle the two responses embebed in (v)MMN. The most popular approach is through the usage of an equiprobable sequence (see Fig. I 9; Barto et al., 2013; Stefanics et al., 2014) and it consists in the presentation of different stimuli with the same probability. It enables the comparison between the response to the deviant stimulus in an oddball sequence to the same stimulus when presented with the same probability in a sequence with many different stimuli.

There is a lack of vMMN research in animals, as -to the best of our knowledge- there is only one published vMMN study performed on monkeys (Kaliukhovich and Vogels, 2014). This study also used the equiprobable condition to infer whether repetition related effects or surprise (genuine) responses are the cause for vMMN. Their results suggest that vMMN is originated from adaptation, at least in monkeys. Apart form this study, there is only speculation in a review (Näätänen et al., 2010), where the authors refer to MMN as a type of automatic sensory intelligence and defend that most of the animal intelligence is based on MMN phenomena, which are essential to the adaptive behaviour of animals in their environment. They give an example about how birds can

anticipate the flying trajectory of another bird, an example that closely relates with predictions and has already been reported in humans (Hubbard, 2005; Zago and Lacquaniti, 2005).

Moreover, similarly to aMMN, there are deficits in the vMMN responses of patients from a certain clinical population (schizophrenia, mood disorders, substance abuse, neurodegenerative disorders, developmental disorders, deafness, panic disorder and hypertension; for a review see Kremláček et al., 2016). However, the deficits in vMMN measured from electrophysiological data for different disorders are not restrained to certain time intervals or scalp locations.

Other techniques, such as neuroimaging, can and should be used to identify which areas of the brain generate the mismatch response in patients and healthy subjects. The next subsection will describe (v)MMN studies using the most common non-invasive neuroimaging technique (fMRI).

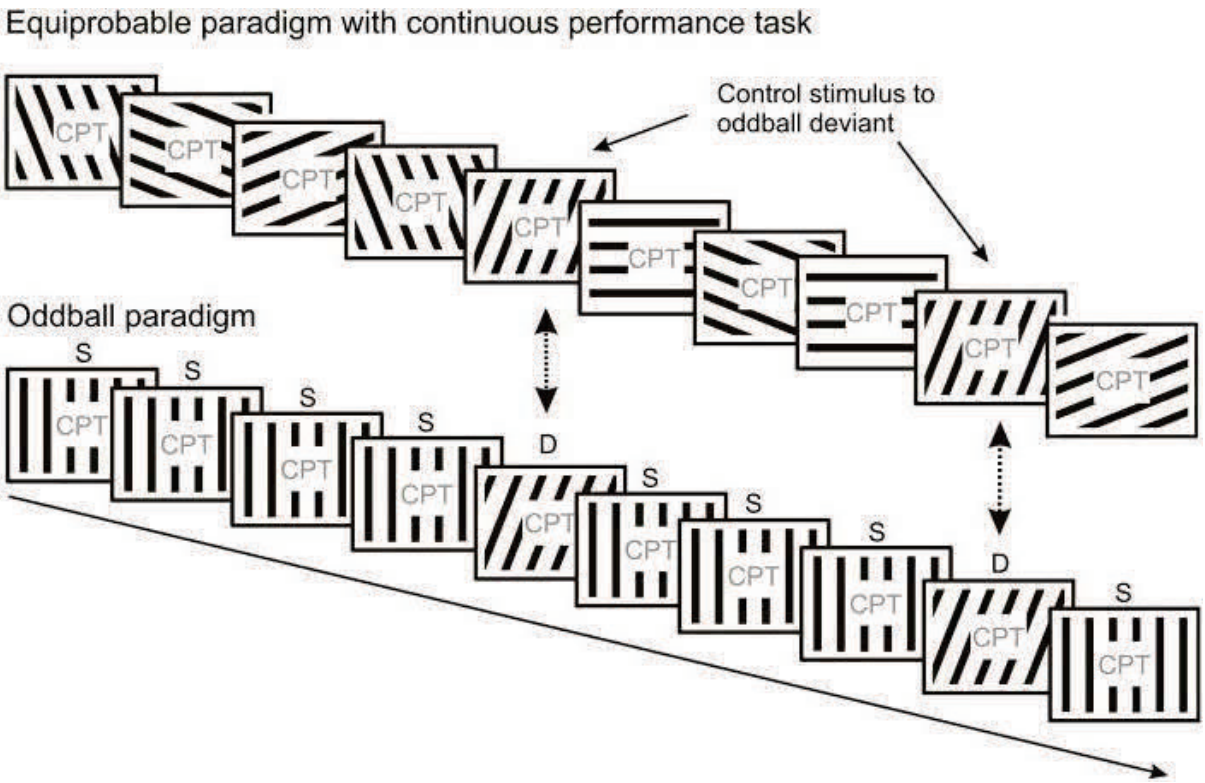

Figure I 9 – Illustration of the equiprobable paradigm. This paradigm can be used as control for oddball paradigms. Each stimulus type occurs with the same probability, normally 10%. The responses elicited by stimuli physically similar to those elicited by deviants (D)/standards (S) in the oddball paradigm can be compared. From Stefanics et al. (2014).

2.2.3 Neuroimaging equivalents of the mismatch negativity

In general, (v)MMN is tested with electrophysiological methods, more specifically EEG. This technique enables to investigate both the spatial and temporal dynamics of MMN. However, EEG studies lead to more conclusions regarding temporal than spatial dynamics (given to its advantageous temporal resolution vs a limited spatial resolution).

Nevertheless, studying the spatial dynamics of MMN is important as it facilitates to identify the generators (i.e. brain regions) of the mismatch response. Several methods can and have been employed to investigate MMN's spatial components, such as single-cell recording (Kaliukhovich and Vogels, 2014), MEG, positron emission tomography (PET), optical imaging (OI) and fMRI (for a review see Deouell, 2007).

Still, from these methods only MEG and fMRI are non-invasive. On one hand, fMRI experiments imply an environment full of loud noises created by the MRI scanner, creating an interaction between these noises and the presented auditory stimulus sequence, which might affect the results by masking some stimuli more than others (Shah et al., 2000; Talavage and Edmister, 2004; Talavage et al., 1999). Note that this interaction is crucial only to auditory MMN. It is possible to overcome this obstacle using MRI sequences and sparse designs that leave a silent period between image acquisitions, allowing a more precise sound presentation (Edmister et al., 1999; Hall et al., 1999). MEG also used to involve noisy environments; however recent machines have high shield ability against the noise, in a way that the experiments can be performed with an open door (Toyomura et al., 2011).

On the other hand, given to its source reconstructions, MEG has a poorer spatial resolution than fMRI (Singh et al., 2002) and, therefore it is considered to be the best non-invasive method to access which brain regions generate the (v)MMN signal. Of

course, the simultaneous application of fMRI and EEG techniques can lead to more detailed information about the spatial and temporal dynamics of MMN.

Until now, only a few auditory MMN studies have used fMRI to investigate and detect the neural background of MMN (Gomot et al., 2006; Hedge et al., 2015; Molholm et al., 2005; Deouell, 2007). Only two studies applied both EEG and fMRI methods to investigate the temporal and spatial dynamics of (v)MMN (vMMN - Hedge et al., 2015; aMMN - Liebenthal et al., 2003).

In general, most of the (v)MMN studies using fMRI reported activations in the frontal cortex, more specifically in the middle frontal gyrus, in the right precentral gyrus and in the medial frontal region (Deouell, 2007). Besides, these frontal regions, the superior temporal gyrus also revealed (v)MMN related changes of the BOLD signal (Gomot et al., 2006; Hedge et al., 2015; Liebenthal et al., 2003; Tse and Penney, 2008).

3 Predictive Theories

The brain needs some method to efficiently process the incoming sensory information, given its constant flow and large magnitude. Especially, if we consider that the brain consumes 20% of the human body energy (Mink et al., 1981) and about 80% of this energy is devoted to the generation of action potentials and postsynaptic potentials (Attwell and Laughlin, 2001). Predictive theories are the most popular and accepted way to explain the energy-efficiency behind neuronal information processes. According to them, the central system can be considered as an inference machine, in the way that perception actively generates and optimizes sensory predictions.

In this section, the central concepts of these theories are described (3.1. Generative models and Bayesian interference), as well as the biological implementation of the early concepts (3.2. Predictive Coding Framework). Finally, the last subsections will focus on explaining how predictive theories provide a proper explanation of the neuronal-phenomena described in section I 2 (RS and MMN, here in the subsection 3.3. and 3.4., respectively).

'Experience is an empirical knowledge, that is,
a knowledge which determines an object through perceptions.'
Immanuel Kant

3.1 Generative models and Bayesian interference

The central concepts of predictive theories hail from early perception science (Helmholtz, 1863). Over a century ago, Helmholtz described the perception as a process of unconscious inference (Helmholtz, 1867), in a way that sensory contents are determined not only by our senses, but also by our previous experiences. Because the information available from the sensory organs is not sufficient to reconstruct the surrounding environment, certain properties have to be inferred from uncertain cues based on experience, with such inferences being explained probabilistic arguments. Both, the collection of experiences that are long out of consciousness and the present sensory impression affect perception, which is the product of unconscious inferences based on evidence that are usually reliable. Helmholtz's inferential view was firstly rejected, but recently it has become widely accepted (Friston, 2005; Kersten et al., 2004; Summerfield and de Lange, 2014).

During the last years, ideas from neuroscience and computer vision research converged and originated the formulation of Helmholtz's inferential view using generative models (Kersten et al., 2004; Knill and Pouget, 2004; Lee and Mumford, 2003; Yuille and Kersten, 2006). Within this context, the generative model is an internal model of the world that serves as basis for inference (MacKay, 1995). This model is constructed through experience and serves to make inferences about the causes of the perceived sensory input, therefore it follows that perception is achieved through inverse inference.

Such generative models are usually formulated with the help of Bayesian probability theory (Bayes and Price, 1763). In this case, hierarchical neuronal processes induce the adaptation of the generative models (the internal model of the world) to match sensory input. Therefore, prior expectations (i.e. generative models) are not stable, but rather continuously recalculated from sensory data (Friston, 2005). The

prior knowledge (also known as 'prior') is combined with incoming sensory information to infer the most probable interpretation of the data (also known as 'posterior'). This is translated into the Bayes equation for the posterior probability p($S|I$) of the sensory source S, given the new evidence/input I (that is, the inverse inference):

$$p(S|I) = \frac{p(I|S)p(S)}{p(I)}$$

Where:

- p(I) is the probability of occurrence of the input I and is used as a normalizing factor;
- p(S) is the prior knowledge, that is, the probability of occurrence of this source S prior to receiving the input I;
- p(I|S) is the model for generating inputs I given the source S (direct inference); this parameter can also be called 'likelihood'.

In the empirical Bayesian formulation, both p(I|S) and p(S) are based on the statistical regularities of the environment and learnt by experience. Figure I 10 exemplifies these processes in terms of object perception.

Bayes' formula means that the perception is a combination of the sensory input and prior knowledge. However, the perceptual content can be driven more intensely by the sensory input or by the prior knowledge, depending on their relative strength. When the sensory input is highly ambiguous or imprecise, perception becomes strongly determined by prior knowledge and context. Whereas, when the prior knowledge is not well-developed or is not precise enough, sensory input determines the posterior and, therefore, the perception (Adams et al., 2013).

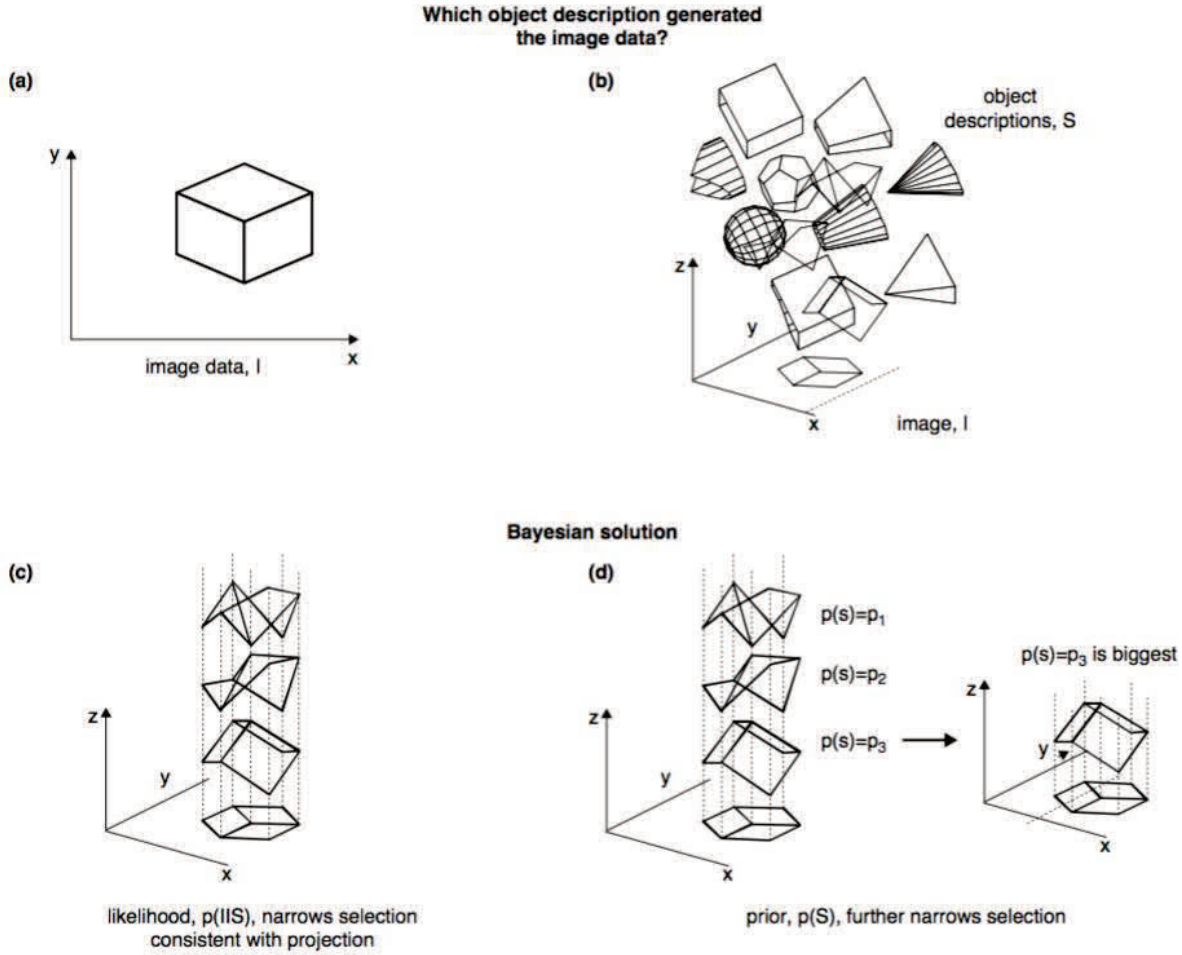

Figure I 10 - Representation of Bayesian object perception. (**a**) Which 3D object caused the image I? The likelihood constrains the possible set of objects consistent with the image I (**b**) The prior knowledge limits the compatible set of 3D objects to those that are more plausible in the world. (**c,d**) The posterior probability is determined by the product of the likelihood and prior knowledge. From Kersten et al. (2004).

Interestingly, there is already evidence suggesting human perception as a product of optimal Bayesian inference with priors generated from the outside world (Jazayeri and Shadlen, 2010; Knill, 1998; Schrater and Kersten, 2000). For instance, orientation judgments under conditions of uncertainty are biased towards cardinal (horizontal and vertical) orientations, which can be explained with a stronger internal prior for these orientations (Girshick et al., 2011). Overall, these findings suggest that the brain accomplishes its perceptual inference through Bayesian processes.

3.2 Predictive Coding Framework

The most plausible biological implementation of empirical Bayes is predictive coding (Friston et al., 2003; Mumford, 1992; Rao and Ballard, 1999). In this model, perceptual inference occurs as an iterative matching process of top-down predictions against bottom-up signals along the cortical hierarchy. According to this framework, feedforward connections process and test prior hypotheses by projecting an error signal which is the mismatch between the predicted and the actual sensory input, or in other words the amount of sensory evidence that cannot be "explained away" by the prior hypothesis. The prediction error is then used to fine-tune the internal generative model through an iterative process, which occurs until the prediction error is removed, so that the model optimally represents the causes of sensory stimuli according to prior experience with the sensory world.

Moreover, predictive coding (PC) is the idea that the generative model of the world is represented in the brain itself. The model is used to constantly predict incoming sensory input and is continuously updated to match the inputs. To do so, predictions are created in higher cortical areas and then transmitted to lower sensory areas through feedback connections between hierarchically organized neuronal populations. Therefore, each region in the cortical hierarchy represents both predictions and sensory input. Neighboring regions are constantly interacting in order to notify each other about what they anticipate and how the higher-level predictions match their own inputs. According to this view, each cortical sensory region consists of two functionally different sub-neuronal populations: a representation unit and a prediction error unit. Representation units form the hypothesis about the forthcoming inputs, while prediction error (PE) units represent the mismatch between those predictions and actual sensory inputs (Fig. I 11). The PEs capture how "surprising" an event is and

signal the representation units to adjust accordingly. Different neuronal populations incorporate different unit groups. For example, superficial pyramidal cells signal the prediction error and deep pyramidal cells sent out the predictions. These processes take place iteratively in form of feedforward and feedback loops throughout the sensory cortices hierarchy. The goal of these loops is to reduce the prediction error, so that the sensory ambiguity is resolved and the predictions encoded at each level of the hierarchy represent current sensory inputs as accurately as possible (Friston, 2005; Pearl, 1988a, 1988b).

Ultimately, these concepts have been described under the unifying brain theory of the free-energy principle (Friston, 2005, 2010). This theory states that "any self-organizing system that is at equilibrium with its environment must minimize its free energy" (Friston, 2010). Free-energy can be described as the amount of active prediction error units. It follows then, that the minimization of free-energy is what provides the brain to approximate to a Bayesian ideal model (3.1.) through inference and learning processes. Under these terms, perception serves the goal of minimizing free energy and is a consequence of the dynamic exchange with the environment.

In the last decade, the concept of predictive coding has been validated by several brain imaging studies investigating predictive feedback and the processing of prediction errors (Alink et al., 2010; Bar, 2007; Egner et al., 2010; Ouden et al., 2010; Rauss et al., 2011; Smith and Muckli, 2010; Summerfield et al., 2006a; Todorovic et al., 2011a). Neural correlates of predictive coding have been highlighted in brain regions as early as the lateral geniculate nucleus (Jehee and Ballard, 2009) and as high-level as the FFA (Egner et al., 2010) or even the frontal cortex (Summerfield et al., 2006a). Empirical support for the predictive coding model has also been found in monkeys (for review see Egner and Summerfield, 2013). For example, non-human primate studies reveal that the visual cortex is a hierarchical system (Felleman and Van

Essen, 1991; Zeki and Shipp, 1988), which is one of the requirements of PC. Additionally, neuroimaging studies (Alink et al., 2010; Egner et al., 2010; Ouden et al., 2010) and single-cell recording experiments (Meyer and Olson, 2011) show that neuronal responses are larger for surprising stimuli when compared to expected stimuli, as PEs are more active when surprising stimuli is present (this phenomenon has been termed expectation suppression, ES; Todorovic and Lange, 2012).

As PC is now presented as a general theory of brain function (see Friston et al., 2009), it has been proposed to explain low-level (e.g. saccadic suppression and filling-in at the blind spot; see Ehinger et al., 2015; Raman and Sarkar, 2016) and high-level phenomena (hysteria and schizophrenia; see Adams et al., 2013; Edwards et al., 2012). Such predictive theories provide a coherent and unified explanation of the neuronal-phenomena described in the subchapter 2 of the Introduction (RS and MMN). The next subsections will focus on how the PC can explain both RS and MMN.

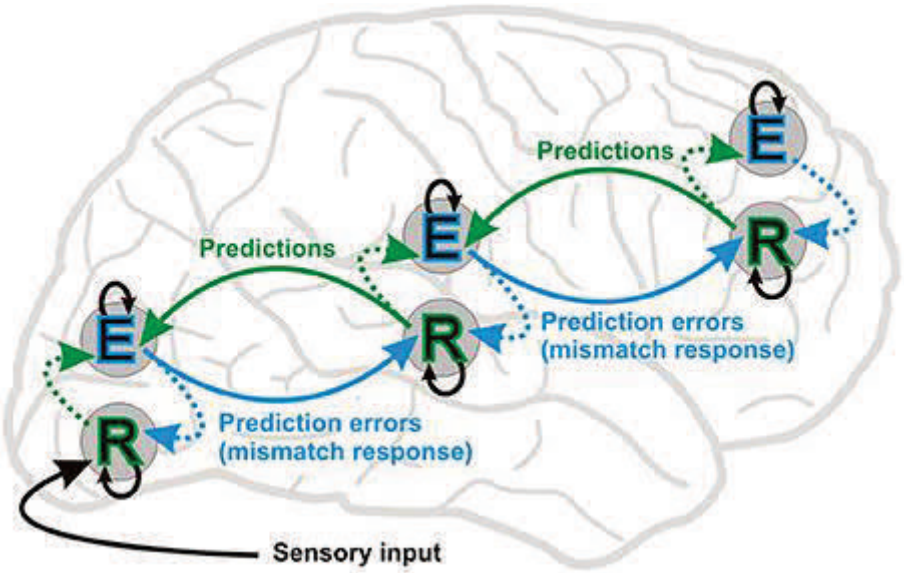

Figure I 11 – Schematic of the predictive coding framework. The scheme depicts the message passing between the neurons in a hierarchical structure (here consisting of three levels) containing feedback and feedforward loops. In order to optimize perception, representation units (R) send out predictions about upcoming input (through top-down connections) and error units (E) return the prediction error, i.e. the mismatch between the received predictions and the sensory input (via bottom-up forward connections). Representation units receive input from error units (E) at the same level (dotted lines) and lower hierarchical levels. Error units receive input from representation units in the same level and the level above. Inhibitory connections are depicted in black arrows. From Friston (2005, 2010) and Stefanics et al. (2014)

3.3. How can predictive theories explain repetition suppression?

Several theories have been used to explain the neuronal mechanisms underlying repetition related phenomena (Fig. I 12). This phenomenon was originally considered to be a consequence of low-level, local mechanisms, such as fatigue, facilitation or sharpening (for reviews see Gotts et al., 2012b; Grill-Spector et al., 2006a). Briefly, the fatigue model describes that all neurons showing initial responses to a stimulus suffer a response reduction to the repetition of this stimulus (Fig. I 12 A). According to this model, synaptic depression induces the response reduction is proportional to the initial neuronal response. Whereas the facilitation model explains RS due to a faster processing of the repeated stimuli, which, through synaptic potentiation, produce shorter latencies or reduced durations of neuronal firing (Fig. I 12 B). Finally, the sharpening model proposes that neurons which responded intensely to the first exhibition of the stimulus will keep their activity upon repetition, while the neurons that responded weakly to the initial presentation will have weaker activity to subsequent presentations of the stimulus (Fig. I 12 C). A fourth explanation for repetition related phenomena is the synchronization model (Fig. I 12 D) which postulates that repetition induces a synchronous coupling between selective neuronal cells, leading to efficient neuronal processes (Gilbert et al., 2010; Gotts et al., 2012).

All the models described above can be fundamentally explained within the predictive coding framework (Auksztulewicz and Friston, 2016; Ewbank and Henson, 2012; Friston, 2012; Grotheer and Kovács, 2016; Henson, 2012). The synchronization between neuronal regions might represent the update of the representation units, which are expressed simultaneously throughout the hierarchy (in high and low areas).

Upon repetition and following subsequent updates, the predictions become more accurate, creating sharper neuronal responses and facilitating them (Henson, 2012).

Given the stability of our visual environment (scenes and objects are usually constant and rarely change; Dong and Atick, 1995), it is important to point out the possibility that repetition is encoded as a 'default' prior (i.e. as the most fundamental form of predictions; Pajani et al., 2017) in the brain. This 'default' prior of repetition would be more evident in the absence of specific expectations (e.g. moving objects or visual transitions) about future events. However, it is still unclear to which extent the presumed 'default' repetition prior can be modulated.

In the following subsections, direct evidence that RS is a consequence of the 'default' prior of repetition will be presented under a two-stage model (Grotheer and Kovács, 2016). In the following sections, I will present how RS is modulated by statistical probabilities and how repetition and expectation phenomena are two independent predictive processes.

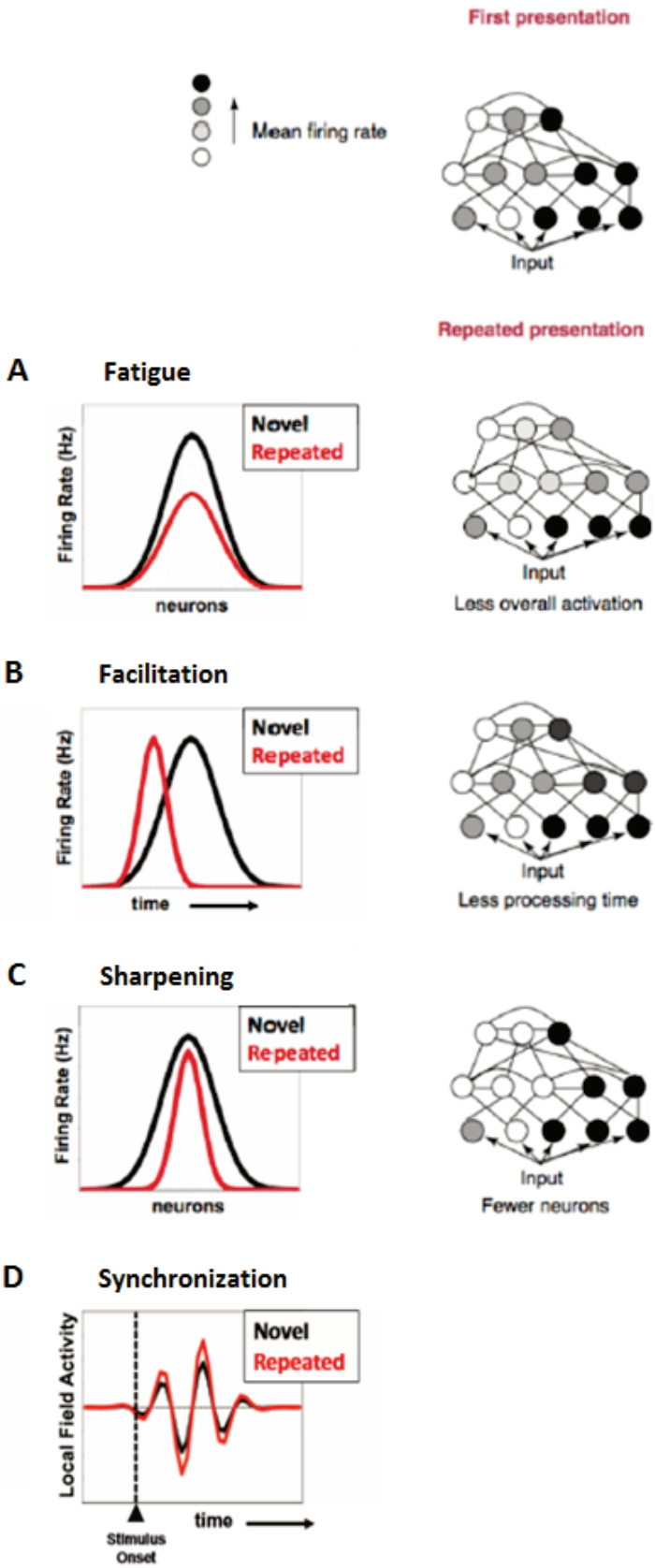

Figure I 12 – Schematic of the repetition suppression models. **Left**: Hypothetical neuronal responses to novel and repeated presentation of a stimulus are depicted in black and red curves, respectively. **Right**: illustration of a neural network that has 3 cortical processing stages. All the 5 models predict a decrease in the neuronal firing rates to repeated stimuli, but for different reasons: **A**. overall fatigue of the neuronal population (Fatigue Model); **B**. shorter duration of neural processing (Facilitation Model); **C.** fewer neurons responding (Sharpening Model); **D**. synchronization of neuronal responses at stimulus onset (Synchronization Model). Adapted from Gotts et al. (2012) and Grill-Spector et al. 2006).

3.3.1. Probability based expectations

There are many ways to signal the future appearance of a given event and thereby elicit predictions and expectations related to it. One way is to manipulate the probabilistic occurrence of events. Summerfield et al. (2008) studied the influence of such probability-based expectations in RS by presenting pairs of faces that could either be repeating (repetition trials, Rep) or alternating (alternation trials, Alt) in blocks that alternated between high (75%, RB) or low (25%, AB) repetition probabilities (Prep). The results revealed enlarged RS in the fusiform face area (FFA; Kanwisher et al., 1997) in blocks where repetitions were more frequent (RB) and therefore more predictable when compared to blocks in which repetitions were surprising due to less frequent repetitions (AB). These results indicate that contextual probability-based expectations of higher-order stimulus statistics modulate RS and can be interpreted in the context of predictive coding theories (Friston, 2005; Rao and Ballard, 1999).

The existence of Prep modulation on RS was confirmed by other studies using faces (Grotheer & Kovács, 2014a; Kovács et al., 2012; 2013; Larsson & Smith, 2012) or letters of a familiar alphabet (Grotheer and Kovács, 2014). However, objects (Kovács et al., 2013) and unfamiliar characters (Grotheer & Kovács, 2014b) did not show Prep modulation on RS, suggesting that repetition probability modulations depend on prior experiences (see Mayrhauser et al., 2014 for a different interpretation). Nonetheless, the way expectations were manipulated in these studies depended directly on the trial type and therefore, on RS. Thus, the mixed block and trial based–design of these experiments does not allow the independent testing of expectation and repetition effects. Moreover, all of the above experiments elicited expectations by probability manipulations and implicitly as (1) no specific instructions were given about the different repetition probabilities of the presented blocks, (2) a concurrent and

orthogonal task was used to draw subjects attention away from stimulus repetition and probabilities and (3) no participant ever reported awareness of these probability dissimilarities after the experiments and no behavioural correlate of these effects was found. It is of note that the Prep modulation of RS is not entirely automatic, as this modulation is disrupted when attention is distracted away from the stimuli (Larsson and Smith, 2012).

3.3.2. Cue-based expectations

It is also possible to induce explicit perceptual expectations on a trial-by-trial basis by establishing associations between cue and a forthcoming stimulus (Egner et al., 2010; Meyer & Olson, 2011). Such cueing paradigms have been employed with stimulus pairs in MEG (Todorovic and Lange, 2012) and neuroimaging studies (Grotheer & Kovács, 2015), in a way that the first stimulus of a pair indicates the probability of forthcoming features (Egner et al., 2010) or the probability of stimulus repetitions or alternations. These studies showed the independence of repetition and expectation effects.

In order to account for these recent results, Grotheer and Kovács (2016) proposed a two-step model of response suppression. According to this model, RS and ES are defined as independent expressions of predictive mechanisms. Additionally, RS is the expression of lower-level error computations when compared with ES. Under this framework, the computations underlying RS takes place in the local circuits, while ES results from the influence of higher-level predictions (see Auksztulewicz and Friston, 2016).

3.4. How can predictive theories explain mismatch negativity?

Similarly to repetition suppression, several hypotheses had previously been proposed to explain the phenomenon of MMN as well. According to the model-adjustment hypothesis (Näätänen and Winkler, 1999; Winkler et al., 1996), the MMN is a manifestation of adjustments in the perceptual model, which occurs when the sensory input does not match the expectations of the model. On the other hand, the adaptation hypothesis (Jääskeläinen et al., 2004; May et al., 1999) proposes that the MMN mirrors adaptative changes in post-synaptic sensitivity during learning. The predictive coding framework accommodates both of these interpretations (Auksztulewicz and Friston, 2016; Baldeweg, 2007; Garrido et al., 2009b).

The MMN response is supposed to signal the violation of the registered rules of the environment, even in the absence of conscious awareness of such regularities (Czigler, 2007; Czigler and Winkler, 2010). The sequence of steps used to explain MMN as a consequence of predictive coding mechanisms are the following: 1. There is an implicit registration of the environment; 2. The registration of the environment is saved; 3. The representation of the environment is constantly compared with the incoming sensory information; 4. (v)MMN responses are created when there is a mismatch between the representations units and the sensory input. Therefore, the MMN component is considered a direct example of predictive error processes (Garrido et al., 2009b).

Empirical evidence that (v)MMN is a consequence of predictive processes exists (Grimm and Schröger, 2007; Lieder et al., 2013a, 2013b, Wacongne et al., 2012, 2012; for reviews see (Garrido et al., 2009b; Paavilainen, 2013b; Stefanics et al., 2014b, 2016). Grimm and Schröger (2007) found that the amplitude of the MMN was related to the specific temporal occurrence of the frequency deviance rather than the global

probability of the frequency deviance. These results support the idea that the MMN system operates on the basis of a spectrotemporal representation rather than on independent feature dimensions. Another study tested the validity of the predictive coding hypothesis with higher-order MMN on omission trials (Wacongne et al., 2011). Their rationale was as follows: 1. the mismatch response should be larger when it is unexpected than when it is expected; 2. a monotonic sequence of five identical tones should elicit a higher-order novelty response; 3. omitting the fifth tone should reveal the brain's hierarchical predictions. The authors reasoned that when a deviant tone is expected, its omission represents a violation of two expectations: a local prediction of a tone and a hierarchically higher expectation of its deviancy. Hence, such omission should induce a greater prediction error than when a standard tone is expected. The results of simultaneous EEE-MEG recordings strongly support the predictive coding hypothesis, as those confirmed the authors' predictions, i.e. a MMN response for the omission of stimulus. The same authors have also proposed a detailed neuronal model to describe auditory MMN, which is based on predictive coding (Wacongne et al., 2012). Further, recent modelling experiments show the potential of predictive coding to provide a complete explanation of the MMN phenomenon (Lieder et al., 2013a). The results of Lieder and colleagues (2013b) reveal that the MMN represents Bayesian learning, and that the MMN-generating processes update the probabilistic model of the environment using prediction errors.

Overall, the predictive coding framework provides a probabilistic account to the conventional views of the MMN. Within this theory, synaptic activity, sensitivity and plasticity are described within the same optimization scheme. Ultimately, the focus on the underlying mechanisms of predictive processes instead of phenomenological description of the neuronal responses might approach adaptation (RS) and MMN (for further comments on this direction see the section III.1).

4 The current studies

This thesis aims to answer the following questions:

II.1: What are the temporal dynamics of expectation and repetition related response suppressions?

II.2: Do expectations affect neural activity by expectation suppression or via surprise enhancement?

II.3: Which neural mechanisms explain vMMN better: surprise related or repetition related responses?

II. 4: What is the relation between the electrophysiological measured vMMN and the signal adaptation in the neuroimaging experiments (fMRIa) within a typical and widely used oddball paradigm?

These questions led to four studies, two of them measured RS using paired stimuli in a within repetition paradigm (same-different), while the other two studies used typical oddball paradigms measuring the electrophysiological phenomenon of MMN. These studies will be presented in the second chapter (II Experiments). All studies included are manuscripts which are either published or are under review. First, the RS studies will be presented and they will be followed by the vMMN studies.

Experiment 1 focuses on the cue-based expectation and RS effects, particularly on the temporal dynamics of expectation and repetition related response. Most studies of ES used a delay-interval between the predictive cue and the target (i.e. the inter-stimulus interval, ISI) in the range of a few hundred milliseconds. While it is known that attentional cueing is strongly affected by the length of the cue-target delay (Busse et al., 2006), there is no information on the temporal dynamics of expectation effects.

In the following experiment the particpants where presented with pairs of faces where the first face could be used to create predictions regarding the second one (in a similar fashion to the sencond experiment). The stimulus pairs were presented with two different ISIs (0.5s for Immediate and 1.75 or 3.75s for Delayed target presentation). The expectation effects were independent of the length of the ISI period, implying that Immediate and Delayed cue-target stimulus arrangements lead to similar expectation effects in the face sensitive visual cortex.

In the Experiment 2, Question2 is addressed by investigating whether expectations affect neural activity by suppressing prediction errors for correctly predicted stimuli (expectation suppression) or via enhancing prediction errors for incorrectly predicted stimuli (surprise enhancement). Repeating or alternating sequences of two faces (where the first face could be used to build expectations regarding the second one) were presented while introducing three conditions (see Kovács and Vogels, 2014): correctly predicted, neutral and incorrectly predicted (surprise condition); BOLD activity ws also collected. We hypothesized that if the expectation effects caused by enhanced PEs in the surprising trials, then the BOLD responses should be larger to surprising trials than to the unpredicted, neutral trials. However, if the prediction effects are due to a response related reduction, (reflecting reduced PEs in the correctly predicted trials), then the BOLD responses should be lower on the correctly predicted trials than on the unpredicted, neutral trials. The main finding is that activity in right FFA appears to reflect surprise enhancement and not expectation suppression, as activity in incorrectly predicted trials is higher than the neutral condition

Since both the Prep modulation of RS and the phenomenon of vMMN are explained on the basis of predictive coding and occur under comparable circumstances (which are related to the regularities of the environment), the Experiment 3 aimed to

unveil possible connections between vMMN and Prep modulations of RS. Considering the fact that the presence of RS dependency on Prep varies with stimulus categories (Kovács et al., 2013), we focused on four probe stimuli, which could (faces and real characters) or could not (chairs and false characters) induce Prep modulation of RS in functional neuroimaging experiments. To test for differences of vMMN between stimulus categories, the stimuli were arranged in two pairs (1. Faces vs Chairs and 2. Real vs False Characters) and presented following a conventional oddball paradigm. Additionally, an equiprobable control condition was used to better understand the neural mechanisms behind vMMN. We hypothesized that these neural mechanisms would co-vary congruently among stimuli according to the existence of Prep modulation of RS in fMRI experiments. In other words, we expected similar underlying neural mechanisms of vMMN within stimulus categories. Another aim of this experiment was to disentangle which neural mechanism explains vMMN better (Question 3): the surprise related response enhancement given the presentation of rare deviants or RS related responses to the frequent presentation of the standards. To answer this question the responses to the stimuli presented in a conventional oddball sequences were compared to the same stimuli in equiprobable sequences (Kaliukhovich and Vogels, 2014). We hypothesised that the observed vMMN would stem from repetition related-phenomena if the standards responses are different than from those in the equiprobable condition, whereas the vMMN could be explained by a surprise enhancement if the deviant responses are different from those in the equiprobable condition (Kaliukhovich and Vogels, 2014). We found significant vMMN for each of the 4 stimulus categories, meaning that the neural mechanisms behind this phenomenon are category dependent but not as assumed on the basis of neuroimaging experiments: the vMMN of faces and chairs was driven by RS; whereas the vMMN of real and false characters was mainly due to surprise-related changes, although RS

could also explain certain vMMN in separate time windows for these stimulus categories.

Experiment 4 investigated the correlation of the MMN effects for character stimuli in EEG and fMRI recordings. A long tradition of electrophysiological studies, using oddball sequences, have shown that neural responses to a given stimulus differ when the presentation occurs frequently (standards) when compared to rare, infrequent presentations (deviants). Even though the repetition of a stimulus also leads to the reduction of the blood oxygen-level dependent (BOLD) signal (fMRI adaptation, fMRIa) when compared to stimulus alternation in fMRI experiments. So far, no study compared the vMMN to fMRIa within the same paradigm and participants in selective regions to the presented stimuli, in this case character-selective. In this study fMRI and EEG data was recorded for characters from the same participant (on different sessions) with an oddball paradigm. As both fMRIa and MMN are related to predictions about the environment, the possible connections between them were put to test (Question 4) and a significant correlation between MMN (CP1 cluster at 400 ms) and fMRIa (letter form area, real characters) was found, supporting their relationship.

II Experiments

1 Similar expectation effects for immediate and delayed stimulus repetitions

This section is a slightly adapted version of the manuscript written by Prof. Dr. Gyula Kovács, Nadine Wanke, Mareike Grotheer and me, that has been submitted to Biological Psychology.

Main research question:

What are the temporal dynamics of expectation and repetition related response suppressions?

Abstract

A prior cue or stimulus, which allows predicting the future occurrence of an event, reduces the associated neural activity in several cortical areas. This phenomenon is termed as expectation suppression (ES) and has recently been shown to be independent of the generally observed effects of stimulus repetitions (repetition suppression, RS: reduced neuronal response after the repetition of a given stimulus) (Grotheer & Kovács, 2015). While it has been shown that attentional cueing is strongly affected by the length of the cue-target delay, we have no information on the temporal dynamics of expectation effects, as in most prior studies of ES the delay between the predictive cue and the target (i.e. the inter-stimulus interval, ISI) was in the range of a few hundred milliseconds. Hence, we presented participants with pairs of faces where the first face could be used to build expectations regarding the second one, in the sense that one gender indicated repetition of the same face while the other gender predicted the occurrence of novel faces. In addition, we presented the stimulus pairs with two different ISIs (0.5s for Immediate and 1.75 or 3.75s for Delayed ISIs). We found significant RS as well as a reduced response for correctly predicted when compared to surprising trials in the fusiform face area. Importantly, the effects of repetition and expectation were both independent of the length of the ISI period. This implies that Immediate and Delayed cue-target stimulus arrangements lead to similar expectation effects in the face sensitive visual cortex.

Keywords: expectation; fMRI adaptation; prediction; repetition suppression; inter-stimulus interval

1. Introduction

Repetition related phenomena have been widely studied using both electrophysiological and neuroimaging techniques. Typically these studies report a suppression of the neural signal for repeated when compared to alternating stimuli (repetition suppression, RS; Henson & Rugg, 2003; for review see Grill-Spector, Henson, & Martin, 2006). RS might reflect a range of mechanisms (i.e. short-term plasticity, network dynamics and biophysical changes of the neural response) and became one of the most intensively studied phenomena in the cognitive neurosciences. Further, it is broadly applied as a tool to investigate the selective properties of neuronal populations in neuroimaging experiments (Malach, 2012).

Recently, the neural mechanisms of RS have been connected to predictive coding theories of sensory perception (PC, see Auksztulewicz & Friston, 2016; Friston, 2005). According to models of PC the brain constantly generates predictions about sensory inputs and then computes the difference between these predictions and the actual sensory input. Therefore, surprising/incorrectly predicted events cause higher neural activity than expected/correctly predicted events (Friston, 2005, 2010; Friston & Kiebel, 2009). In other words, the occurrence of an expected event can also lead to reduced neuronal activity when compared to incorrect predictions, i.e. to surprising events. This phenomenon was recently termed as expectation suppression (ES, Todorovic & Lange, 2012).

In an influential study, Summerfield et al., 2008 presented participants with pairs of faces which could either repeat or alternate. These faces were grouped into blocks with either high or low repetition probabilities (P_{rep}). The authors found larger RS in the fusiform face area (FFA; Kanwisher et al., 1997) in blocks where repetitions were more likely, and hence more expected, when compared to blocks with less frequent and

thus surprising repetitions. The authors suggested that higher order contextual expectations modulated repetition-related processes. Later studies confirmed the existence of such P_{rep} modulations of RS for faces (Grotheer & Kovács, 2014b; Kovács et al., 2012; 2013; Larsson & Smith, 2012) and for Roman letters (Grotheer & Kovács, 2014a). While no such modulations were found for chairs (Kovács et al., 2013) or unfamiliar characters (Grotheer & Kovács, 2014b), but for a different conclusion see Mayrhauser et al., (2014). All of these studies used a factorial design in which repetition and repetition probability varied orthogonally. However, they did not allow the independent testing of expectation and repetition effects due to the use of high and low repetition blocks to manipulate expectations.

Other studies have induced explicit perceptual expectations on a trial-by-trial basis by associating a given stimulus with a preceding schematic cue or image (Egner et al., 2010; Meyer & Olson, 2011). Current MEG and neuroimaging studies have combined such paradigms with stimulus repetitions, in the sense that the first stimulus of a pair signals the likelihood of repetitions or alternations, and found both ES and RS to be present in the target related signal (Amado and Kovács, 2016; Grotheer & Kovács, 2015; Todorovic & Lange, 2012). Importantly, both the MEG and the neuroimaging studies have found that the effects of expectation and repetition are independent and additive processes in the human brain.

Earlier studies have explored the influence of the inter-stimulus interval (ISI) length on RS and showed similarities between short and long-lagged repetition effects (Henson et al., 2004; Sayres & Grill-Spector, 2006), but it has also been suggested that different neuronal mechanisms explain RS for long and short ISIs (Epstein et al., 2008; Kouider at al., 2009; Larsson & Smith, 2012; Weiner et al., 2010). Additionally, both electrophysiological (Feuerriegel et al., 2015) and behavioral (Matthews, 2015) studies

of RS and repetition priming have reported distinct effects of stimulus duration and ISI variability. Moreover, it is also known that ISI length affects attentional cueing as well (Busse et al., 2006, Hansen and Hillyard, 1980).

In spite of the demonstrated effects of ISI on RS and on attentional cueing, previous studies which have investigated ES invariably used short (in the range of few hundred milliseconds) delay-intervals between the predictive cue and the target (Amado and Kovács, 2016; Egner et al., 2010; Grotheer & Kovács, 2015).

Since we have no information on the temporal dynamics of cue-based expectation effects (Matthews & Gheorghiu, 2016), the aim of the current study was to investigate whether additive effects of RS and ES are consistent across changes of the repetition delay. To this end, we used the methods, task and paradigm of Grotheer & Kovács (2015) with different ISI lengths. To anticipate our results, we observed significant RS and ES in the FFA, but we did not find any interaction between ES and RS for either ISI conditions, suggesting that the length of ISI does not influence the neural mechanisms of ES and RS.

2. Materials and Methods

2.1 Participants

Twenty-six healthy Caucasian volunteers participated in the experiment. No participant reported any neurological or psychiatric illnesses and all subjects had normal or corrected to normal visual acuity and gave written informed consent in accordance with the protocols approved by the Ethical Committee of the Friedrich-Schiller-University Jena in accordance with the Declaration of Helsinki. Overall, three participants were excluded from the final analysis. One was excluded due to excessive head-movements (i.e. translation/rotation of >5 mm/degrees) during the recording, while another participant failed to perform the experimental task properly (the performance was below 50% in one experimental run) and one participant interrupted the recording session. Therefore the current report is based on the data of 23 participants (17 females; 20 right-handed, mean age (±SD): 21.6 (0.7) years).

2.2 Stimulation and Procedure

Stimuli were 300 gray-scale, digital photos of full-frontal Caucasian faces (2.75° visual angle.), identical to those of Grotheer & Kovács (2015). Briefly, stimuli were fit behind a circular mask, placed in the center of the screen on a uniform black background. Stimulus pairs were presented, with 250 ms exposition time for each stimulus. We only used Caucasian faces as it is known that the own race bias results in differences regarding the perceptual expertise with own when compared to other-race faces (for review see: Meissner & Brigham, 2001). Two inter-stimulus intervals (ISI) were used. In the *Immediate* condition the ISI was 500ms, and hence identical to that of previous publications (Amado and Kovács, 2016; Grotheer & Kovács, 2015). In the

Delayed condition the ISI was varied randomly between 1.75 and 3.75 seconds (this temporal jitter was introduced to help the separation of the BOLD response, related to S1 and S2). The two ISI trial types were presented in two separate runs in an order randomized across participants. The inter-trial intervals were randomized between 1s and 3s or between 3.75s and 5.75s for the *Immediate* and *Delayed* conditions, respectively (see Fig.E1.1). This relatively short time-range for the *Delayed* ISI condition was chosen because the further elongation of the ISI (to the order of minutes) would have led to an experiment-duration up to two hours. Two runs were recorded from each participant (one for each ISI condition) and no stimulus occurred in more than one trial during a given run. The runs contained 180 trials and lasted for about 11 and 25 minutes for the *Immediate* and *Delayed* conditions, respectively. Stimuli were back-projected via an LCD video projector (NEC GT 1150, NEC Deutschland GmbH, Ismaning, Germany, with modified lens for short focal point) onto a translucent circular screen, placed inside the scanner bore (stimulus presentation was controlled by Matlab R2013a (The MathWorks, Natick, MA, USA), using Psychtoolbox (Version 3.0.9)).

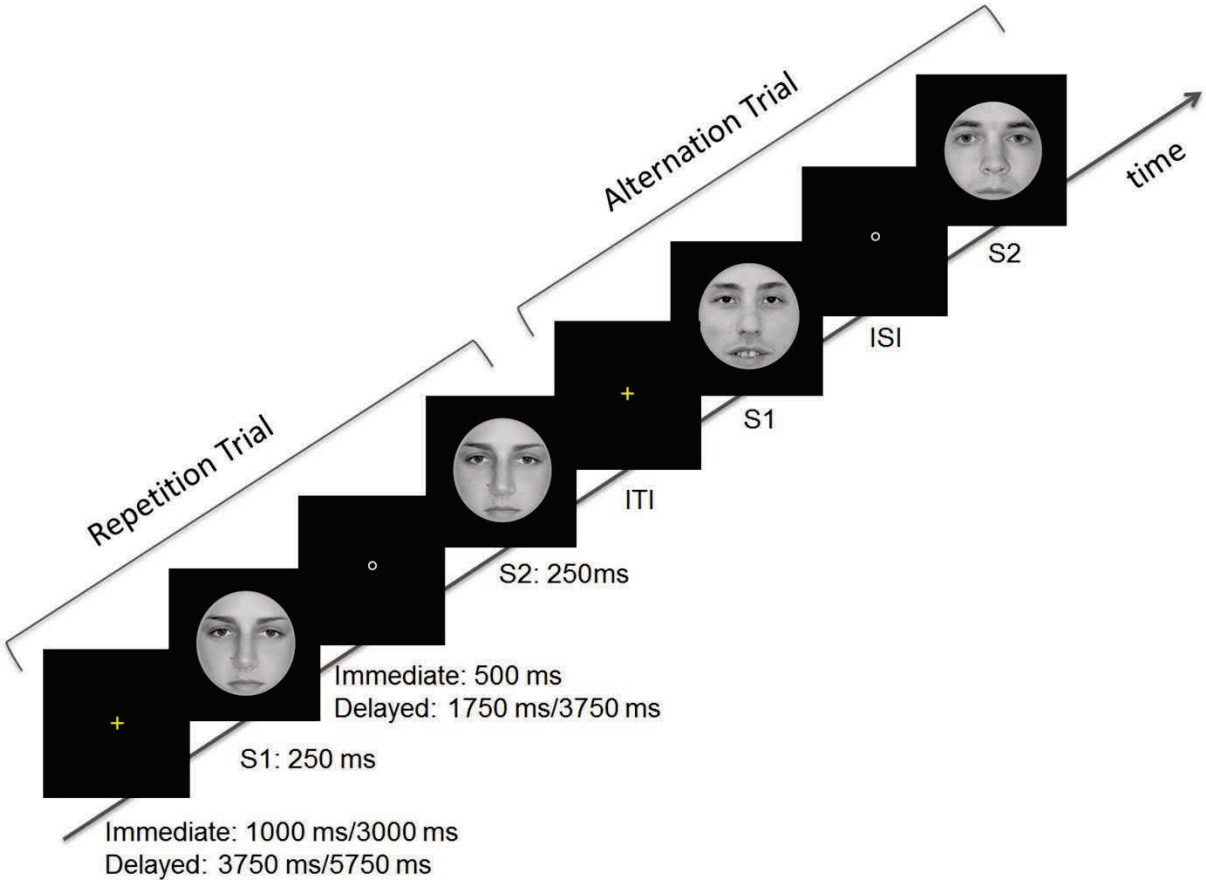

Figure E1.1 - Overview of the stimulation parameters and arrangements. At the beginning of each trial, a yellow fixation cross was presented for 1 or 3 s in the *Immediate* ISI condition and for 3.75 or 5.75 s in the *Delayed* ISI condition. The cross was followed by the predictive cue, S1, which was shown for 250ms. During the ISI a small white circle appeared on the screen. The ISI conditions correspond to *Immediate* and *Delayed* lengths of fix 500ms and varying 1.75/3.75s, respectively. Finally, the target, S2, was presented for 250ms. Note that *Immediate* and *Delayed* trials were given in separate runs

Trial structure and design were identical to those of Amado and Kovács (2016) and Grotheer & Kovács (2015). Briefly, we used a paired stimulus presentation where the predictive cue, the first stimulus (S1), could either be different (Alternation Trial (Alt)) or identical (Repetition Trial (Rep)) to the second, target stimulus (S2). To reduce local feature adaptation the size of either S1 or S2 (chosen randomly) was reduced by 18%. Both stimuli of a pair were either female or male and participants were presented with 50% female/male trials randomly. The gender of S1 cued stimulus repetition or alternation to the participants probabilistically. In other words, the likelihood of repetition/alternation was contingent on the gender of S1. The cue could represent high (75%) or low (25%) probabilities of repetition/alternation of the target stimulus (S2). For example, for half of the subjects, female faces signaled high repetition probability (75%), while male faces signaled high alternation probability (75%). Thus, for these subjects 75%/25% of the female/male faces were repeating while 25%/75% of the female/male faces were alternating. This way, participants could form expectations regarding the likelihood of repetitions and alternations. Correctly predicted trials correspond to a congruence between the given cue (S1) and the repetition/alternation occurrence during S2 (75% of the trials), whereas the incorrectly predicted, or surprising trials correspond to an incongruency between the given cue (S1) and the repetition/alternation occurrence during S2 (25% of the trials). The relationship between face gender and repetition probability was counterbalanced across participants, in a way that for the other half of the subjects the gender cueing high repetition probability was male and the relative repetition probabilities were reversed accordingly (75%/25% of male/female faces were repeated and 25%/75% of the male/female faces were alternating). Participants were informed about the relative repetition/alternation probabilities as well as about their contingencies on the face gender of S1 prior to the scanning sessions. In addition, participants performed a 5-

minute long training session (using stimuli that were different from those used in the main experiment) immediately prior to the fMRI recordings.

Moreover, following the method of Larsson & Smith, (2012), 20 (11.1% of the trials) additional blank trials were included in each run in order to enable the estimation of the average response time course to the target stimulus (S2) alone. In these trials, S1 was normally displayed and instead of S2, a blank screen was presented. This way, an estimate of the average response time course to S2 alone was obtained by performing a subtraction between the blank trials and the experimental conditions which included S2 and S1 as well. In order not to bias the predictions of participants, these trials had an equal amount of female and male faces for S1. Importantly, the overall probabilities for the correctly predicted and surprising conditions were of 66.7% and 22.2%, respectively. As the introduction of the blank trials made the separation of subsequent trials perceptually more difficult, the color of the fixation cross was changed to yellow before the presentation of S1, to clearly mark the beginning of trials.

In total, we had five different experimental conditions, presented randomly within a run: expected repetition (E_Rep), expected alternation (E_Alt), surprising repetition (S_Rep), surprising alternation (S_Alt) and blank (Blank) trials. Figure E1.2 illustrates the experimental design.

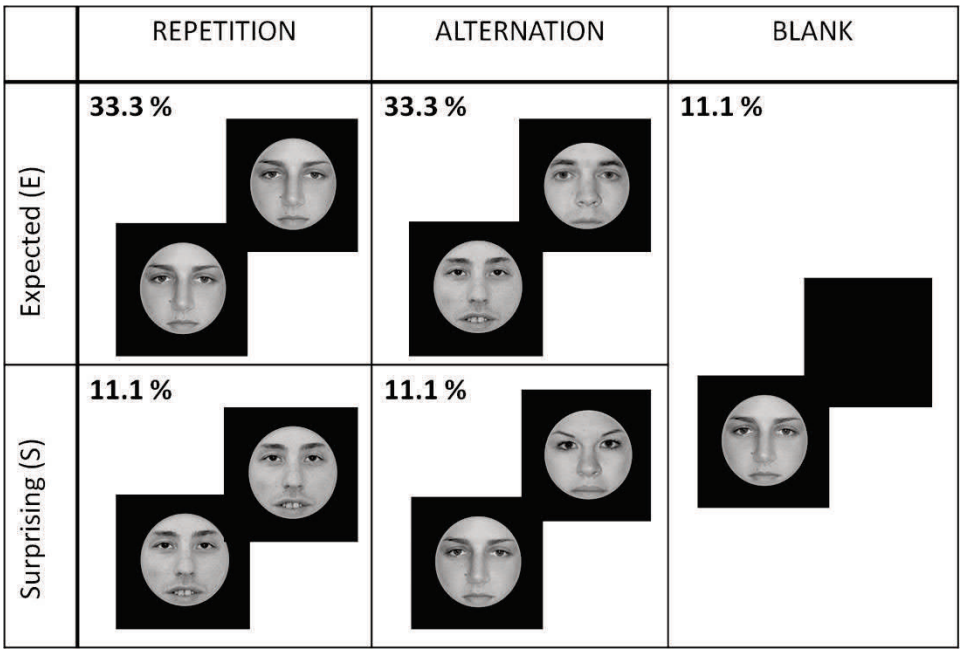

Figure E1.2 - Experimental design and conditions. Each face gender signaled different repetition/alternation probabilities (high or low) randomly for every participant. Here we present an example where the face gender signaling high repetition probability was female (E_Rep), while male faces cued high probability of alternations (E_Alt). Male/female faces signaled low probability of repetitions/alternations (S_Rep/S_Alt). Blank trials contained either female or male faces, randomly

To control participants' attention and to confirm that they are able to judge the stimulus gender effectively, 18% of the trials were target trials in which subjects had to report whether the S1 had been a female or male face by pressing a button (Todorovic & Lange, 2012). Therefore, for these target trials, a choice-screen was presented for 2 seconds centrally showing either the text "*female ? male*" or "*male ? female*", randomly. The choice-screen appeared 1 sec after S2 was blanked out. A small color change of the fixation cross functioned as feedback regarding their answers (green for correct and red for incorrect responses).

2.3 Imaging Parameters and Data Analysis

Imaging was done with a 3-Tesla MR scanner (Siemens MAGNETOM Prisma fit, Erlangen, Germany). T2* weighted images were collected using an EPI sequence (35 slices, 10° tilted relative to axial, TR =2000 ms; TE = 30 ms; flip angle = 90°; 64 x 64 matrices; 3mm isotropic voxel size). A high-resolution T1-weighted 3D anatomical image was acquired using a MP-RAGE sequence (TR = 2300 ms; TE = 3.03 ms; 192 slices; 1 mm isotropic voxel size).

Details of preprocessing and statistical analysis were described previously (Cziraki, Greenlee, & Kovács, 2010). The functional images were realigned, normalized to the MNI-152 space, resampled to 2 x 2 x 2 mm resolution and spatially smoothed with a Gaussian kernel of 8 mm FWHM (SPM12, Welcome Department of Imaging Neuroscience, London, UK). A separate functional localizer run (640 sec long, 20 sec epochs of faces, objects and Fourier randomized versions of faces, interleaved with 10 sec of blank periods, 2 Hz stimulus repetition rate; 300 ms exposure; 200 ms blank) served as basis for Regions of Interest (ROIs) detection. ROI creation was performed with MARSBAR 0.44 toolbox for SPM (Brett, Johnsrude, & Owen, 2002). Only those individuals in whom the respective ROIs could be identified in both hemispheres were included in the further analyses. The FFA was determined individually as an area responding more intensely to faces than to objects and Fourier randomized versions of faces ($p<0.0001_{UNCORRECTED}$). Its location could be identified reliably and bilaterally in 20 participants [average MNI coordinates (±SE): 41 (0.6), -54 (1.3), -19 (0.8) and -41 (1.4), -57 (1.7), -18 (0.7); average cluster size (±SE): 72(7), 52(5) voxels; for the right and left hemispheres, respectively].

A time series of the mean voxel value within the areas of interest was calculated and extracted from our event-related sessions using custom made scripts and Marsbar. The

convolution of each of the 5 experimental conditions (E_Rep, E_Alt, S_Rep, S_Alt, Blank) with the canonical hemodynamic response function (HRF) of SPM12 (Welcome Department of Imaging Neuroscience, London, UK) was used to define predictors for a General Linear Model (GLM) analysis of the data. Target trials were not modeled separately, as there was sufficient time between the end of the trial and the choice-screen presentation. Thus the BOLD signal of the S2 was not affected by the button presses or by the choice-screens. Note that the subtraction between Blank trials and the other experimental conditions (E_Rep, E_Alt, S_Rep, S_Alt) was executed to estimate the average response time course to S2 alone (Larsson & Smith, 2012). We performed repeated measures ANOVAs for the FFA activity separately with hemisphere (2), expectation level (2, E and S), trial type (2, Alt and Rep) and ISI condition (2, Immediate and Delayed) as factors. Post-hoc analyses were executed using Fisher LSD tests.

3. Results

3.1 Behavior

Participants required on average 981 ms (±SD: 45 ms) to determine the gender of the presented S1 faces. Reaction times did not differ significantly between trial types ($F(1,22)=1.15$, $p=0.29$, $\eta p^2=0.05$), expectation levels ($F(1,22)=0.24$, $p=0.63$, $\eta p^2=0.01$) or ISI conditions ($F(1,22)=2.22$, $p=0.15$, $\eta p^2=0.09$). Similarly, only tendencies were observed for any of the interactions ($p>0.08$ for all comparisons). This suggests a similar allocation of attention to the different experimental conditions.

Mean accuracy for gender judgement was 86% (±SD: 3%) across all experimental conditions. The participants' accuracies did not differ between trial types ($F(1,22)=1.53$, $p=0.22$, $\eta p^2=0.07$) and ISI conditions ($F(1,22)=1.62$, $p=0.22$, $\eta p^2=0.07$). Further, no significant interactions were observed ($p>0.08$ for all comparisons). Interestingly, and confirming previous results (Amado and Kovács, 2016; Grotheer & Kovács, 2015), there was a strong tendency for a main effect of expectation level ($F(1,22)=3.4$, $p=0.08$, $\eta p^2=0.13$), showing an enhanced accuracy for correctly predicted (M(±SD)=88(3)%) when compared to surprising (M(±SD)=82(5)%) trials.

3.2 Fusiform Face Area

Overall, the results confirmed those of our prior studies (Amado and Kovács, 2016; Grotheer & Kovács, 2015). We observed a significant main effect of trial type (i.e. significant RS; Fig.E1.4; $F(1,19)=25.09$, $p=0.0008$, $\eta p^2=0.57$) with an average signal reduction of 0.1% (equivalent to an average relative signal reduction of 27%). We also found a main effect of expectation level (i.e. significantly higher responses for surprising as compared to correctly predicted events: $F(1,19)=5.65$, $p=0.028$, $\eta p^2=0.23$). On average the correct predictions led to a signal reduction of 0.05% (corresponding to an average relative signal decrease of 16%) when compared to the incorrect predictions. No main effect of hemisphere was found ($F(1,19)=1.27$, $p=0.27$, $\eta p^2=0.06$). Additionally, the effects of trial type and expectation level did not interact with each other ($F(1,19)=3.08$, $p=0.10$, $\eta p^2=0.14$), but were additive (Fig. E1.3).

More important to the aims of the current study, we did not find a significant main effect of ISI condition ($F(1, 19)=1.68$, $p=0.21$, $\eta p^2=0.08$). There was neither an interaction of ISI condition with the effect of trial type ($F(1, 19)=0.37$, $p=0.54$, $\eta p^2=0.02$) nor with the effect of expectation ($F(1, 19)=1.2$, $p=0.28$, $\eta p^2=0.06$). The four-way interaction of the hemisphere, ISI condition, trial type and expectation was not significant either ($F(1, 19)=0.53$, $p=0.48$, $\eta p^2=0.03$). This suggests that both RS and the effect of expectation are independent of the length of the ISI period.

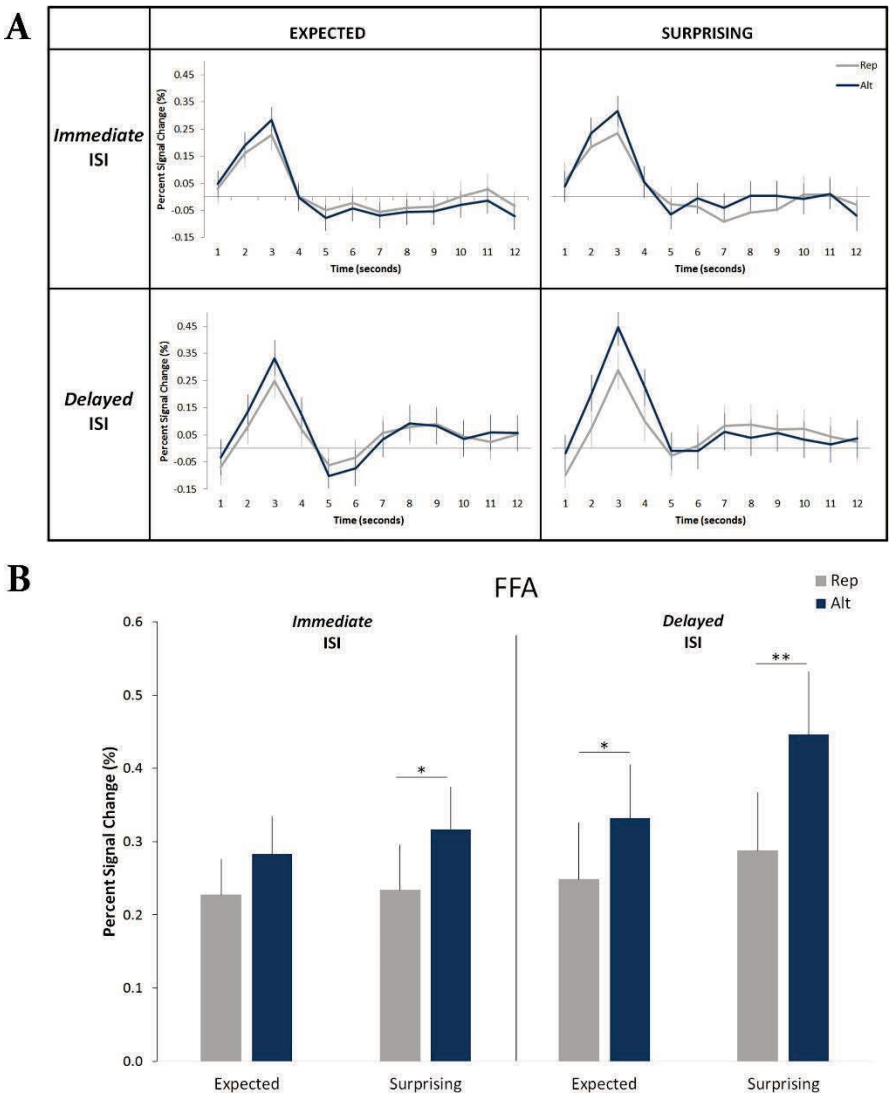

Figure E1.3 - Effects of expectation and repetition on the FFA responses (averaged left and right hemispheres) for different ISI conditions. a. Average response time course for Rep and Alt trials in expected (correctly predicted; left) and surprising (incorrectly predicted; right) events for the *Immediate* (up) and *Delayed* (down) ISIs. b. Percent-signal changes (±SE) are presented separately for trials types, expectation levels and ISI conditions. ** $p<0.001$ * $p<0.05$

3.3 Whole-brain analysis

It is theoretically possible that expectation and repetition effects are encoded elsewhere in the brain. Hence, we performed a second level whole-brain analysis testing for the main effects of RS, ES, ISI and the interaction of these factors, using a fixed threshold of $p<0.05_{FWE}$, with a cluster size>50 voxels. Testing the main effect of ISI (*Delayed>Immediate*) revealed an active cluster in the early visual cortex (MNI [x,y,z]: 4, -86, 20; cluster size: 288), while the opposite contrast (*Immediate>Delayed*) led to several regions with significant activations (Table E1.1). The whole-brain analysis did not reveal additional active clusters when testing for the main effects of RS and ES or for the interactions between ES, ISI and RS.

In order not to overlook any activation on the whole-brain level (however, see the recent discussion, initiated by Eklund et al.(2016) about the inflated false-positive rates of such cluster analyses) we also applied a more liberal $p<0.0001_{uncorrected}$ threshold with a smaller cluster size (>20 voxels). Both the *Immediate>Delayed* and the *Delayed>Immediate* contrasts showed some additional regions with significant activations (Table E1.1). Yet, once again, no additional active clusters were found when testing for the main effects of RS and ES or for the interactions between ES, ISI and RS, supporting the results of the ROI analysis.

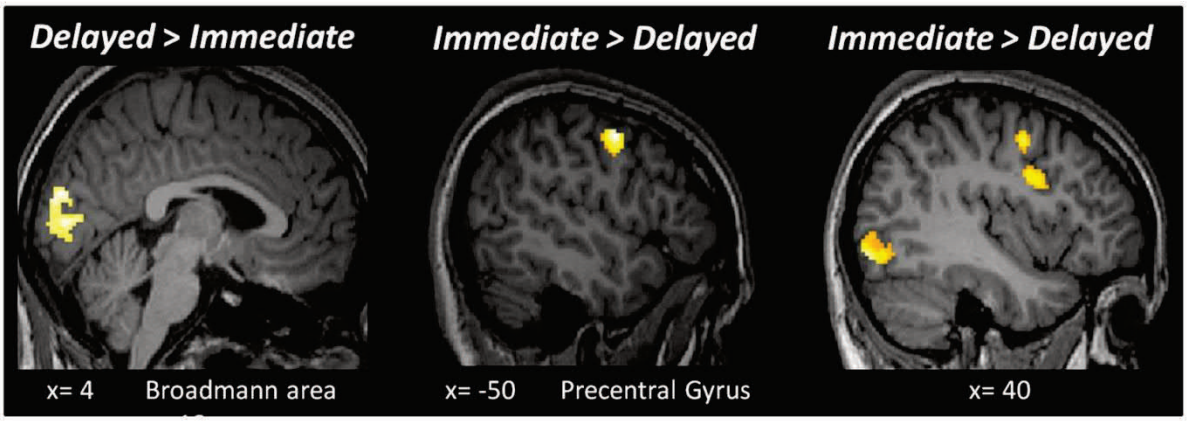

Figure E1.4- Results of the whole-brain analysis with a fixed threshold of $p<0.05_{FWE}$, with a cluster size bigger than 50 voxels for the following contrasts: Delayed > Immediate and Immediate > Delayed

Table E1.1 - Summary of significant activations in the whole-brain analysis

Contrast	Brain Region	Coordinates	Cluster size	Threshold
Delayed >Immediate	Broadmann area 18	4, -86, 20	288	(p<0.05 FWE)
Delayed >Immediate	Inter-Hemispheric	0, -62, 56	57	(p<0.0001 unc)
Delayed >Immediate	Broadmann area 6	56, -4, 6	23	(p<0.0001 unc)
Immediate>Delayed	Precentral Gyrus	-50, -4, 48	241	(p<0.05 FWE)
Immediate>Delayed	Inferior Occipital Gyrus	40, -84, -10	405	(p<0.05 FWE)
Immediate>Delayed	Broadmann area 6	50, 2, 48 6, 8, 54	481 143	(p<0.05 FWE) (p<0.05 FWE)
Immediate>Delayed	Sub-Gyral	28, -50, 46	67	(p<0.05 FWE)
Immediate>Delayed	Lingual Gyrus	-18, -88, -8	211	(p<0.05 FWE)
Immediate>Delayed	Middle Frontal Gyrus	-28, -5, 54	61	(p<0.0001 unc)

4. Discussion

We observed significant repetition and expectation effects in the FFA in the form of reduced responses for repeated and expected stimuli, respectively. These effects were found to be additive and independent of the length of ISI and imply that *Immediate* and *Delayed* predictive cueing produce similar effects of expectation related response suppression in the FFA, suggesting that the observed expectation effects survive a several second long time-interval. The fact that RS and ES were found to be additive and thereby independent from each other for both ISI lengths confirms the results of recent studies that used short ISIs (Amado et al., 2016; Grotheer & Kovács, 2015; Todorovic & Lange, 2012).

4.1 Repetition Suppression

Earlier RS studies, using different ISI lengths, have suggested that RS is stable over short cue-target periods (in the range of 250ms to 4s) for object stimuli (Henson et al., 2004; Sayres & Grill-Spector, 2006), which is in accordance with our major result.

On other hand, these (Henson et al., 2004; Sayres & Grill-Spector, 2006) and other studies proposed the existence of dissimilarities in the neuronal mechanisms of RS for long (maximum of 8 min) and short (less than 3s) ISIs as well. Epstein (2008) reported that RS differences due to ISI length depend on the viewpoint of visual scenes (in range of 500ms to 8min, for short and long ISIs, respectively), in other words short-interval RS was only significant when scenes were repeated from the same viewpoint, while long-interval RS was less viewpoint-dependent. Furthermore, Weiner (2010) used objects as stimuli and showed that RS varies quantitatively across time periods in the ventral temporal cortex. This study used ISI categories which are somewhat different from those used in the current study: the short and the long ISI periods were of 500ms to 3s and of 1s to 174s, respectively. Therefore, in the study of Weiner (2010) there was an overlap of durations in the short and long ISI conditions, which was not present in the current study. Additionally the maximum length of their "short" ISI is comparable to our *Delayed* condition. Furthermore, Weiner (2010) used objects as stimulus and did not study RS on a trial by trial basis. All these facts make the comparison of that and the current study difficult.

Face studies have found that a long-lagged condition (ISI in the range of 7 min) is sensitive to face familiarity, in a way that RS is only significant for familiar faces (Kouider et al., 2009). In this study participants had to judge face familiarity. The results revealed that face-processing occurs even without perceptual awareness. Furthermore, different face viewpoints were also investigated, yet no effects of

viewpoint were found for either the familiar or unfamiliar faces. Note that the minimum duration for the long lagged condition was 7min in their study, which is considerably larger than the 3.75s applied in the current study. Importantly, instead of a blank screen, in this study a mask was presented between S1 and S2 to manipulate perceptual awareness. The use of shorter lengths and the absence of this mask in the ISI period might explain why we found RS effects with unfamiliar faces for the *Delayed* condition as well. Also, the current study did not include familiarity as a factor. It will be important to determine what role familiarity plays in expectations and the related RS with specifically designed future experiments that are comparable to those of the study of Kouider et al., (2009). Importantly, Larsson & Smith, (2012) investigated how probability based expectations affect RS with longer ISIs and showed that Prep modulation of RS exists with longer (4s) cue-target periods but it also depends on attention. These findings are in accordance with our results, despite the fact that Larsson & Smith, (2012) induced expectations implicitly, based on the differential probabilities of trials within blocks, while here expectations were manipulated explicitly, with a cue, on a trial-by-trial basis.

A recent electrophysiological study has investigated not only how RS varies with different ISI periods but also how it is influenced by diverse stimulus presentation durations of S1 and S2 (Feuerriegel et al., 2015). Their results indicate no effect of ISI period on the N170 amplitudes for faces or chairs. However, the positive P2 component showed the lowest amplitudes following the shorter ISI. As is known, electroencephalography provides advantages with regard to the temporal resolution in comparison with the fMRI technique and this fact can possibly explain incongruences between that and the current studies. Therefore, further electrophysiological studies are also necessary to evaluate how expectation effects modulate RS in different cue-target stimulation periods.

4.2 Expectation

Notably, no ISI effects were observed on the behavioral data or on the BOLD signal. Busse (2006) reported reaction time facilitation for expected events that were presented with short cue-target stimulus periods. These differences can easily be explained by the number of trials and the use of different stimuli by the current and this behavioral study, which used moving dots and arrows for stimulation.

Another behavioral study inspected how time perception depends on different durations for stimulus presentation and ISI (Matthews, 2015). Following the paradigm of previous studies (Summerfield et al. 2008, Larsson & Smith, 2012), this behavioral study used the probabilities of repetitions in each block to manipulate expectations. Interestingly, repeats were judged longer than novel items for shorter ISIs, but this effect was more pronounced when the repetitions were rare. For the longer ISI condition repeated and novel images were judged the same. This extensive study included several experiments and among them there is also one in which expectations were manipulated explicitly by signaling the repetition status of the forthcoming stimuli (similar to what is done in the current study). Interestingly, in this case no differences were found between the temporal judgment of novel and repeated stimuli, reinforcing the existence of neuronal processing differences between implicit and explicit expectations. However this work did not test how temporal perception is affected by ISI period when expectations are explicit (note that the participants' task was to judge the duration of S2 in these experiments).

The fact that we found similar ES for the *Immediate* and *Delayed* conditions is in line with theories of predictive coding (Friston & Kiebel, 2009, PC). PC explains the brain as a cascadic system of parallel feed-forward and feedback processes in which the sensory information is continuously compared to the current expectations of the

system, based on prior experiences, and only the difference of the two, the predictive error, is propagated to higher-level areas (Friston, 2010). The predictive error is calculated and updated continuously in such a system. Whether there is an upper time-limit of the influence of the predictive stimuli is still an open question. Our results, however, suggest that the effect of the calculated predictions is not only manifest for immediate subsequent phenomena but it also extends to a time range of several seconds, increasing the stability of the system.

4.3 Possible ISI variability effects

In addition, we also know that the frequency or pace of events is a crucial parameter for the creation of expectations. A central timing system, also referred to as "pacemaker", describes that the pace/frequency of the event occurrences enables the creation of temporal perception units (Zakay & Block, 1997). Furthermore, it has been proposed that these local temporal perception units feed information to central systems (Matthews, 2015) and probably have an important role in prediction generation as well. Summerfield and colleagues (2011), in an electrophysiological study, investigated how the stimulus repetition consistency influences expectation and RS using stable (30-40 trial long) and volatile (10 trial long) blocks of stimulus presentations. Note that expectation was manipulated by the use of different repetition probabilities in these blocks. Their results showed a modulation of expectations on RS at central electrodes for the stable, long blocks, while no modulation was present for the volatile, shorter blocks. As stability over time can play a role in expectation related effects (mentioned as well by PC theories as the time-variability effects, see Friston, 2010), it would be important to test possible effects of ISI variability and the ISI length, independently. Here we only had one long variable and one short constant ISI condition. Therefore further experiments are necessary to disentangle these two distinct effects (variability and length).

4.4 Whole brain analysis

The results obtained by the whole-brain analysis are in line with the previous studies that propose different neuronal mechanisms for short and long lagged cue-target stimulation periods. The results show several brain activation differences between the *Immediate* and the *Delayed* ISIs. Yet no significant differences between these two conditions were found in the FFA. Moreover, the whole brain analysis did not elicit main effects of trial or expectation conditions which were previously found by Amado and Kovács (2016) and Grotheer & Kovács (2015). The lack of these effects in the present study might be due to the lower number of trials in comparison with the former studies. Furthermore, the possibility that activation differences found between the *Immediate* and the *Delayed* ISIs are dependent on the different variability levels (constant and variable) cannot be excluded.

4.5 Conclusion

In conclusion, this study shows that RS and expectation effects in the FFA are independent and additive processes for both *Immediate* and *Delayed* ISIs. As no significant difference was found between the two ISI lengths in the FFA, we can conclude the effects of repetition and expectation are maintained for several seconds in the FFA.

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2 The contribution of surprise to the prediction based modulation of fMRI responses

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Main research question:

Do expectations affect neural activity by expectation suppression or via surprise enhancement?

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The contribution of surprise to the prediction based modulation of fMRI responses

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ABSTRACT

In recent years, several functional magnetic resonance imaging (fMRI) studies showed that correct stimulus predictions reduce the neural responses when compared to surprising events (Egner et al., 2010). Further, it has been shown that such fulfilled expectations enhance the magnitude of repetition suppression (RS, i.e. a decreased neuronal response after the repetition of a given stimulus) in face selective visual cortex as well (Summerfield et al., 2008). Current MEG and neuroimaging studies suggest that the underlying mechanisms of expectation effects are independent from these of RS (Grotheer and Kovács, 2015; Todorovic and Lange, 2012). However, it is not clear as of today how perceptual expectations modulate the neural responses: is the difference between correctly predicted and surprising stimuli due to a genuine response reduction for correctly predicted stimuli or is it due to an increased response for surprising stimuli? Therefore, here we used a modified version of the paradigm of Grotheer and Kovács (2015) to induce predictions independently from repetition probability by presenting pairs of faces (female, male or infant) that were either repeated or alternating. Orthogonally to this, predictions were manipulated by the gender of the first face within each pair so that it signaled high, low or equal probability of repetitions. An unpredicted, neutral condition with equal probabilities for alternating and repeated trials was used to identify the role of surprising and enhancing modulations. Similarly, to Grotheer and Kovács (2015), we found significant RS and significant expectation effect in the FFA. Importantly, we observed larger response for surprising events in comparison to the neutral and correctly predicted conditions for alternating trials. Altogether, these results emphasize the role of surprise in prediction effects.

1. Introduction

The extensively studied neural repetition suppression (RS) phenomenon (for review see Grill-Spector and Martin (2006)) has been recently associated with predictive coding (PC) theories (Friston, 2005) of neural functions (Summerfield et al., 2008). RS describes decreased neuronal response after the repetition of a given stimulus and is used to study the selective properties of neuronal populations (Malach, 2012). Similar to RS, fulfilled expectations also lead to reduced neural activity when compared to incorrect predictions, i.e. surprising events, and this phenomenon has recently been termed as expectation suppression (Grotheer and Kovács, 2015; Todorovic and Lange, 2012). Yet, the relationship between RS and expectation suppression as well as their underlying neural mechanisms are still unclear.

Summerfield et al. (2008) found that the magnitude of RS depends on the probability of stimulus repetitions (Prep): the RS was enhanced in the fusiform face area (FFA; Kanwisher et al., 1997) when faces were presented in blocks in which repetitions were frequent (therefore expected) as compared to when presented in blocks with low repetition probability. Authors suggested that higher-order contextual expectations modulated, via feedback connections, repetition-related processes and interpreted this result in the context of PC models (Friston, 2005; Rao and Ballard, 1999). According to PC, the visual cortex operates under a hierarchical structure where higher areas send predictions about sensory inputs to lower level areas, which then compute the difference between predictions and the actual sensory input (termed as prediction error - ε). To re-estimate and update predictions, ε is forwarded from lower to higher areas of the processing system.

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Consequently, surprising/incorrectly predicted events generate higher neural activity in comparison with correctly predicted events, maximizing the efficiency of neuronal processing (Friston, 2005, 2010; Friston and Kiebel, 2009). Summerfield et al. (2008) interpreted the enhanced magnitude of RS for expected stimuli as the reduced neuronal activity induced by a smaller ε (following Henson (2003) claim of a link between RS and ε). This effect of expectation on RS was later replicated for faces (Grotheer et al., 2014; Kovács et al., 2012, 2013; Larsson and Smith, 2012) and for stimuli of high expertise (Grotheer and Kovács, 2014), while such Prep modulations were not found for object-related RS (Kovács et al., 2013; Mayrhauser et al., 2014) and for unfamiliar characters (Grotheer and Kovács, 2014). It should be noted that all of these above studies used blocks with high and low repetition probabilities to manipulate expectations, for example in blocks with high likelihood of repetition, repeated trials are predicted and alternating trials are surprising while the opposite is true for blocks with low repetition probabilities. Therefore, this mixed design does not allow the independent testing of expectation and repetition effects.

Recently, a MEG study (Todorovic and Lange, 2012) could however, manipulate RS and expectation suppression independently, evoking expectations on a trial-by-trial basis using a preceding cue. Pairs of identical or different tones were presented; the expectations of the subjects were generated by the first tone of each pair, which signaled the likelihood of repetitions with 75% accuracy. The results indicated that expectation suppression and RS have different temporal windows, though an expectancy modulation on repetition effects was also observed. The different mechanisms behind expectation suppression and RS is supported further by Grotheer and Kovács (2015), where pairs of female/male faces were used as stimuli and their gender was signaling the different repetition probabilities (for example female faces were repeated with high while male faces were repeated with a low probability). This fMRI study showed that RS and expectation suppression are additive, rather than interacting in the FFA and the occipital face area (OFA; Gauthier et al., 2000).

However, none of these previous studies could clarify whether the addition of expectation suppression and RS effects is due to a decrease of the response for correctly expected stimuli or an increase of the response to the surprising, unexpected stimuli (Kovács and Vogels (2014) raised this issue and suggested the inclusion of a "neutral" condition with equal probabilities for alternating and repeated trials, in which no expectations are induced (see also Arnal and Giraud (2012) and Rahnev et al. (2011)). Fig.1 illustrates the possible hypotheses regarding RS and expectation modulations of the neural responses, considering the inclusion of the neutral condition. We reasoned that if the previously observed expectation effects are due to a genuine response reduction, then these trials should lead to lower BOLD signal when compared to the unpredicted, neutral trials as well. However, if the prediction effects are due to the enhanced response in the surprising trials (alternating and repeated) then these should lead to larger BOLD responses when compared to the unpredicted (neutral) as well as to the correctly predicted trials. Thus, a main effect of expectation conditions and a subsequent post-hoc analysis would clarify from which expectation condition the BOLD signal of unpredicted, neutral trials differs most – from the correctly predicted (suggesting the role of expectation in predictions) or from the surprising trials (suggesting the role of surprise in predictions). Here we used the methods, task and paradigm of Grotheer and Kovács (2015) with the additional trials of the neutral, unpredicted condition, to study under which circumstances these top-down (suppressing or enhancing) modulations operate.

Anticipating our results, we found significant RS and expectation effect in the FFA. Further, we observed a significant increase of neuronal responses for the surprising, unexpected events, relative to the neutral and unpredicted events in the alternation trials. The relationship of RS and surprise differed between hemispheres: rFFA revealed a dependence of RS on surprise, whereas lFFA showed the independence of these two processes. Overall our results emphasize the role of surprise in predicted processes.

2. Material and methods

2.1. Participants

24 healthy subjects participated in the experiment after giving written,

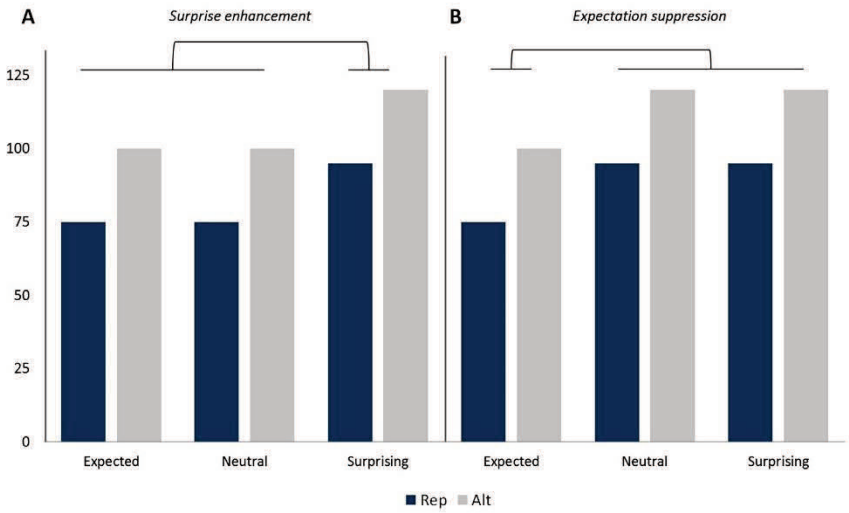

Fig. 1. Illustration of how repetitions and expectations might modulate neural responses. Speculative BOLD responses are presented separately for repeated (Rep) and alternating (Alt) stimuli under correctly predicted, neutral and surprising conditions. (A) Surprising trials (Rep and Alt) lead to elevated BOLD responses when compared to neutral and correctly predicted ones (Rep and Alt), signaling the role of surprise enhancement. (B) Correctly expected trials (Rep and Alt) lead to lower responses when compared to neutral and surprising trials (Rep and Alt), suggesting the role of expectation suppression. Please note the existence of a response difference between fulfilled and violated expectations in the current scheme, as suggested previously (Arnal and Giraud, 2012) and shown by Grotheer and Kovács (2015).

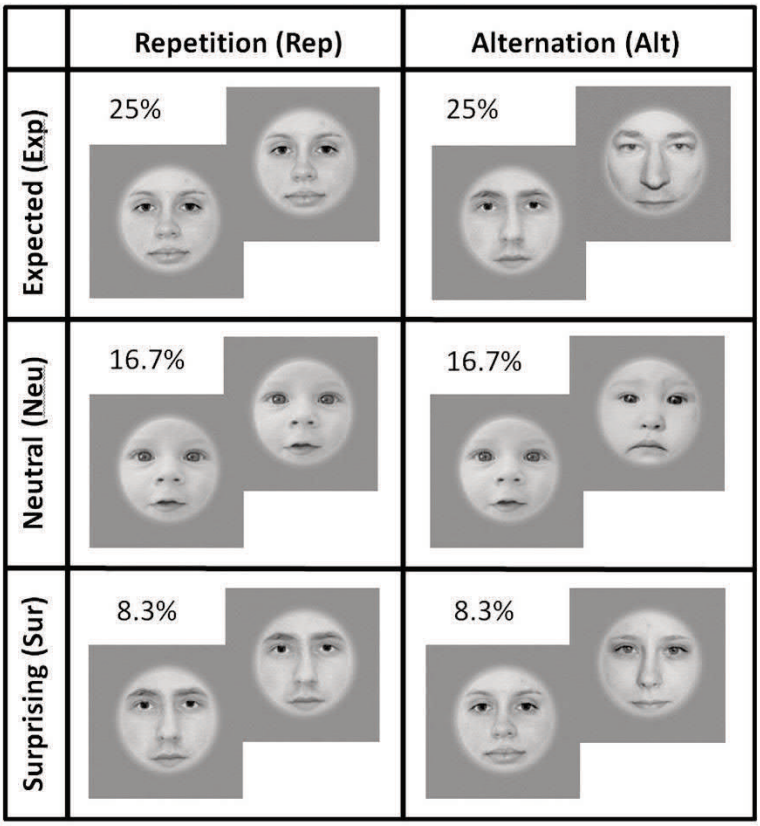

Fig. 2. Experimental design and conditions. Each stimulus category (either infant, male or female faces) was used as a cue to signal different repetition/alternation probabilities (high, low or equal) randomly for every participant. Here we present a situation where the face category signaling high repetition probability was female (Exp_Rep), while male faces signaled high probability of alternations (Exp_Alt). Conversely, male/female faces signaled low probability of repetitions/alternations (Sur_Rep/Sur_Alt). Infant faces indicated equal repetition and alternation probabilities (Neu_Rep and Neu_Alt).

informed consent in accordance with the protocols approved by the Ethical Committee of the Friedrich Schiller University Jena. No participant had any history of neurological or psychiatric illness and all had normal or corrected to normal vision. Due to technical issues, 2 participants were excluded from the analysis and for 1 participant only 2 of the 3 functional runs were acquired. Thus, 22 subjects (8 male; 2 left-handed, mean age (±SD): 23.5 (2.9) years) were involved in the final analysis.

2.2. Stimulation and procedure

The experimental design (Fig. 2) was similar to what has formerly been used to evaluate the relationship between stimulus repetitions and fulfilled expectations (Grotheer and Kovács, 2015), with the exception that two additional trial types were introduced – neutral repetition trials (Neu_Rep) and neutral alternation trials (Neu_Alt). These were corresponding to a previously suggested neutral or unpredicted condition (Rahnev et al., 2011; Kovács and Vogels, 2014) in which the probability of repeated (Rep) and alternated (Alt) trials was identical. The other four conditions were identical to those of Grotheer and Kovács (2015). Briefly, trials were either correctly expected (Exp, high probability) or surprising (Sur, low probability). This conscious expectation was achieved by the fact that the category of the first face (female, male or infant) in each pair signaled with 75% accuracy whether repetitions or alternations were more likely to occur. In other words, the probability of Rep and Alt was contingent with the gender of the first face stimuli. In addition to this and orthogonal to the modulation of expectation, trials could either be repeated or alternating allowing the testing of the independence of expectation and repetition effects. Overall we had six different trial types that were presented randomly within a run: correctly predicted repetition trials (Exp_Rep), correctly predicted alternation trials (Exp_Alt), surprising repetition trials (Sur_Rep), surprising alternation trials (Sur_Alt), neutral repetition trials (Neu_Rep) and neutral alternation trials (Neu_Alt). In all conditions, pairs of female and male faces were either repeating or alternating with an overall probability of 50–50%.

Stimulus presentation was controlled via MATLAB R2014a (The Mathworks, Natick, MA, USA), using Psychtoolbox (Version 3.0.12). 280 grey-scale, digital photos of full-frontal Caucasian adult faces (50% of both genders), similar to the face stimuli of Kovács et al. (2012, 2013) and 140 grey-scale full-frontal digital photos of Caucasian young infant faces aged between 1 and 2 years (collected from the public domain of the world wide web) were placed behind a circular mask and positioned in the centre of the screen on a homogeneous grey background. Stimuli were displayed via an MRI-compatible LCD screen (32' NNL LCD Monitor, Nordic-NeuroLab, Bergen, Norway; refresh rate: 60 Hz) placed at 142 cm from the observer. A total of 3 runs were administered and no stimulus appeared in more than one trial during each run. One run was composed of 240 trials (correctly predicted, surprising and neutral conditions had 120, 40 and 80 trials within a single run, respectively) and took about 13 min. Stimuli were presented for 250 ms each, pairwise, separated by a randomly varied inter-stimulus interval (between 400 and 600 ms with 50 ms steps) and followed by a randomized 1 or 2 s long inter-trial interval. The first stimulus (S1) could either be identical to (Rep) or different from (Alt) the second stimulus (S2). Stimulus size was 6° in diameter. To avoid low level local feature adaptation the size of either S1 or S2 was randomly reduced by 32% in each trial (Grotheer and Kovács, 2014; Summerfield et al., 2008). The same face category was used for each stimulus pair (i.e. both faces of the pair were always either female, male or infant) and subjects were presented with 33.33% female/male/infant trials (administrated randomly). The stimulus category was used as a cue to signal high-, low- or medium- probabilities of trial type (repetition or alternation) occurrences. For example for a given participant female faces signaled high (75%), infant faces signaled equal (50%) repetition probabilities while male faces signaled high (75%) alternation probability. This way participants could form predictions regarding the likelihood of repetitions and alternations (in this example repetitions are predicted when a female face appeared while alternations are predicted when male faces were presented). Importantly, the third face category (in the above example the infant faces) was used as an unpredictive (Arnal and Giraud, 2012) or neutral cue as repetitions and alternations could follow S1 with equal likelihood in this category. The relationship between face category and repetition probability was counterbalanced across participants in a way that each category signaled high/low/equal probabilities with equal probability across participants (to

avoid any possible stimulus effects that could arise due to a different attentional modulation invoked by adult and infant faces – Brosch et al. (2007)). Prior to the scanning session, participants were informed about the relative repetition/alternation probabilities as well as about their contingencies on stimulus category and adequate task performance was assured. During the scanning session, before the 80th and the 160th trial a message appeared on the screen for 10 s to inform participants about the relative repetition/alternation probabilities of the subsequent trials as well as about their contingencies on stimulus category.

To confirm that subjects were paying attention to the stimuli and to guarantee that they were capable of judging the stimulus categories effectively, 18% of the trials were target trials in which subjects had to respond whether the S1 had been a female, male or infant face (Todorovic and Lange, 2012). Therefore, for these target trials 1 s after S2 presentation, a choice-screen was displayed for 2 s showing the different stimulus category options (infant, female and male). The order of the presented options on this choice-screen was counterbalanced across trials. Participants had to indicate their choice by pressing the left, middle or right button. A small color change of the fixation cross functioned as feedback regarding their response (green for correct and red for incorrect answers).

2.3. Imaging parameters and data analysis

Imaging was performed with a 3-Tesla MR scanner (Siemens MAGNETOM Prisma fit, Erlangen, Germany) located at the Research Centre for Natural Sciences (Hungarian Academy of Sciences) in Budapest, Hungary. A T1-weighted high-resolution 3D anatomical image was acquired using a MP-RAGE sequence. The anatomical data had the following parameters: TR=2300 ms; TE=3.03 ms; 192 slices; 1 mm isotropic voxel size. These images were prearranged based on a sagittal localizer to cover the whole brain. fMRI images (T_2*weighted images) were collected using an EPI sequence (34 slices, 10° tilted relative to axial, TR=2000 ms; TE=30 ms; flip angle=90° matrix size=64 × 64; 3 mm isotropic voxel size).

Details of pre-processing and statistical analysis were described previously (Cziraki and Kovács, 2010). Briefly, the functional images were realigned, normalized to the MNI-152 space, resampled to 2 × 2 × 2 mm resolution and spatially smoothed with a Gaussian kernel of 8 mm FWHM (SPM12, Welcome Department of Imaging Neuroscience, London, UK). Independent functional localizer run (640 s long, 20 s epochs of faces, objects and Fourier randomized versions of faces, interleaved with 20 s of blank period, 2 Hz stimulus repetition rate; 300 ms exposure; 200 ms blank) served as basis for Regions of Interest (ROIs) selection, which were analyzed using the MARSBAR 0.44 (Brett et al., 2002) toolbox for SPM. The ROIs were selected individually on the single subject level from the thresholded ($p < 0.001_{uncorrected}$) *t* maps of the contrast *faces vs Fourier randomized faces*. The FFA (N=22), average MNI coordinates (±SE) and cluster sizes (±SE) for left and right hemisphere were the following: −40.4 (0.8) −59.6 (1.3) −17.7 (0.9) and 54(5); 41.6 (0.9) −57.8 (1.3) −16.8 (0.7) and 54(3). The clusters include voxels higher than $p < 0.001_{uncorrected}$ within a 5 mm sphere around the peak voxel. The average locations of these ROIs are presented together with the localizer whole-brain results in Fig.3A.

A time series of the average voxel value within the different ROIs was determined and extracted from our event-related sessions. The convolution of the canonical Hemodynamic Response Function (HRF) of SPM12 with each of the 6 experimental conditions (Exp_Rep, Exp_Alt, Sur_Rep, Sur_Alt, Neu_Rep, Neu_Alt) was used to define predictors for a General Linear Model (GLM) analysis of the data. Target trials were not modelled separately, due to sufficient time between trial and choice screen presentations. Preliminary analyses revealed no main effect of experimental run ($F(2,40)=0.4865$, $p=0.62$, $\eta p^2=0.02$) nor significant interactions between run and trial type ($F(2,40)=1.56$, $p=0.22$, $\eta p^2=0.07$) or conditions ($F(4,80)=1.7$, $p=0.15$, $\eta p^2=0.08$), therefore the results of the three runs were averaged. We performed repeated measures ANOVAs for the FFA with hemisphere (2), expectation condition (3) and trial type (2) as within-subject factors. Post-hoc analyses were performed using Fisher LSD tests.

3. Results

3.1. Behavior

Mean accuracy for gender judgement was 91% (±SD: 8%) across all trial types (Exp_Rep: 93(7)%, Exp_Alt: 94(5)%, Sur_Rep: 84(18)%, Sur_Alt: 88(13)%, Neu_Rep: 92(6)%, Neu_Alt: 90(11)%). The participant's performances did not differ between trial types ($F(1,21)=0.97$, $p=0.34$, $\eta p^2=0.04$). However, participants had a significantly lower performance in trials when their predictions were incorrect (main effect of expectation condition: $F(2,42)=3.8$, $p=0.03$) as compared to trials with correct predictions (Fisher LSD *post hoc* test: $p=0.01$) and a similar trend was seen when compared against neutral trials (Fisher LSD *post hoc* test: $p=0.08$).

On average participants required 1146 ms (±SD: 117 ms) to

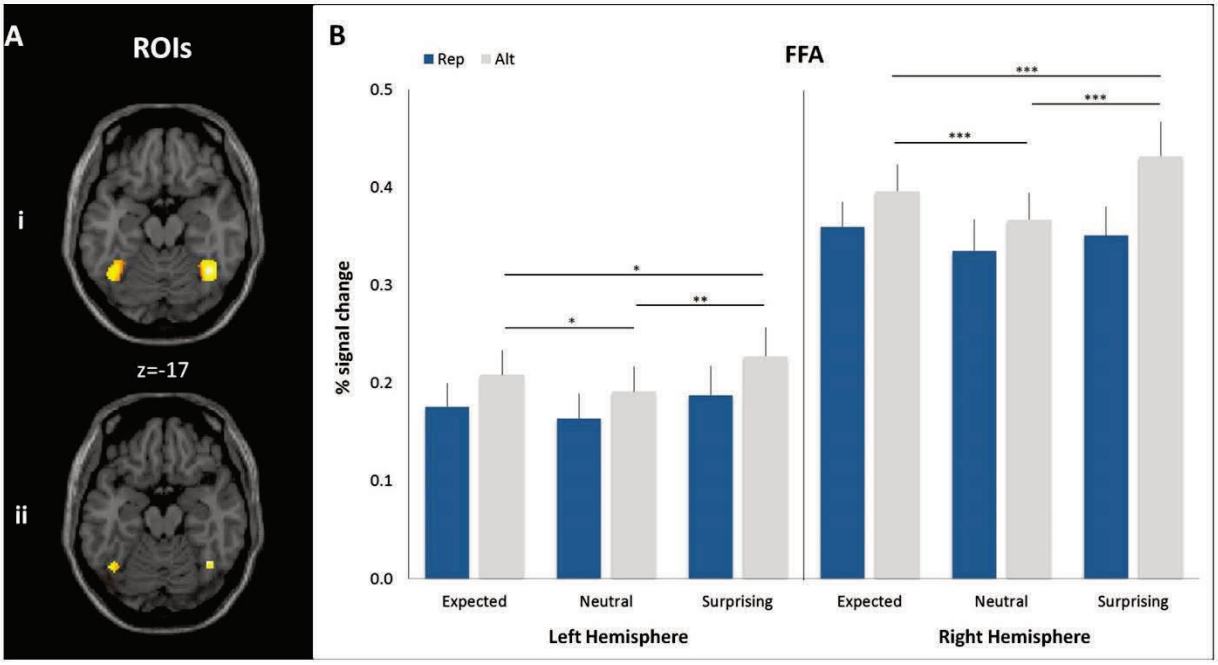

Fig. 3. The location of the left and right FFA and the respective activations in the form of percent-signal change. A. Results of the functional localizer used to determine the location of FFA. i) Average activations contrasting faces and Fourier noise images ($p < 0.05_{FWE}$ with a cluster extent of >50 voxels). ii) A 4 mm sphere around the average peak coordinates of FFA. B. Effects of expectation conditions (E, N and S) and repetitions (Alt/Rep). Percent-signal changes (±SE) of the FFA (left and right hemispheres) are presented separately for trial types and expectation conditions. The RS effects were significant ($p < 0.001$) for all conditions in left and right hemispheres, therefore not marked separately. *$p < 0.05$,**$p < 0.01$,***$p < 0.001$. Rep - repetition trial, Alt - alternation trial.

determine the gender of the presented faces. Reaction times did not differ significantly between trial types ($F(1,21)=0.105$, $p=0.75$, $\eta p^2=0.01$) or expectation conditions ($F(2,42)=0.82$, $p=0.45$, $\eta p^2=0.04$).

3.2. fMRI

3.2.1. FFA

The ANOVA results of this section will be presented in the following order: 1. Main effect of RS; 2. Main effect of expectation condition; 3. Main effect of hemisphere; 4. Interactions.

We observed a significant repetition suppression (Fig. 3B; main effect of trial type: $F(1,21)=26.84$, $p=0.00004$, $\eta p^2=0.56$) with an average signal reduction of 0.04% (equivalent to a relative signal reduction of 14%). We also found a main effect of expectation condition ($F(2,42)=5.09$, $p=0.01$, $\eta p^2=0.2$), which was due to a larger BOLD response for incorrect predictions when compared to neutral, unpredicted events (Fisher LSD *post hoc* test: $p=0.003$). On average the incorrect predictions led to a signal enhancement of 0.04% in comparison with the neutral condition (corresponding to a relative signal increase of 12%), suggesting the role of surprise related response enhancement. Interestingly, a similar tendency was observed when comparing correctly predicted and neutral conditions (Fisher LSD *post hoc* test: $p=0.07$), indicating somewhat smaller overall responses for the unpredicted, equal probability trials as compared to trials with correct predictions. Unlike in our prior study (Grotheer and Kovács, 2015) we found no difference between correct and incorrect predictions (Fisher LSD *post hoc* test: $p=0.2$).

We also observed a main effect of hemisphere ($F(1,21)=20.25$, $p=0.0002$, $\eta p^2=0.49$) in the form of larger BOLD responses in the right, when compared to the left FFA. This hemisphere effect interacted with trial type: $F(1,21)=5.09$, $p=0.04$, $\eta p^2=0.2$), due to a larger RS effect in the right (Fisher LSD *post hoc* test: $p<1e-7$) in comparison with the left hemisphere (Fisher LSD *post hoc* test: $p=4e-5$). Importantly the three-way interaction of trial type × expectation condition × hemisphere was also significant ($F(2,42)=3.38$, $p=0.04$, $\eta p^2=0.14$), meaning that the magnitude of RS showed a dependency on expectation condition and hemisphere. This interaction is mainly due to the higher RS for incorrect predictions over the other conditions for the right FFA. Nonetheless, the repetition effect was significant for all expectation conditions and for both the left and right hemispheres (Fisher LSD *post hoc* tests: $p<0.001$ for all comparisons). Additionally, alternating trials were significantly different for the three expectation conditions for both hemispheres, having the most elevated responses during the surprising events and lower BOLD responses in the neutral and in the correctly predicted conditions (Fig. 3B, Fisher LSD *post hoc* tests: $p<0.05$ for all comparisons).

In order to test the robustness of these results we performed the identical analysis on a smaller, spherical ROI with a diameter of 3 mm. The results of this and the previously presented analysis were identical (with the exception that the three-way interaction of trial type × expectation condition × hemisphere showed only marginal significance), suggesting that the applied criterion has no major effect on it (Table 1).

3.2.2. Whole-brain analysis

To test whether repetition and expectation effects are encoded by other neurons outside the FFA, we also performed a second-level whole-brain analysis testing for repetition and expectation effects as well as for the interaction of these factors, using a fixed threshold of $p<0.05_{FWE}$ with a cluster size >20 voxels. Testing the main effect of repetition (Alt > Rep) revealed one active cluster in the right fusiform gyrus (MNI [x,y,z]: 36, −52, −14; cluster size: 351; see Fig. 4). While not identical with it, this coordinate closely resembles the average coordinate of our rFFA. The opposite contrast (Rep > Alt) led to no significant activations anywhere in the brain. The same threshold yielded two clusters of activations for the Surprising > Expected (Sur > Exp) contrast, revealing higher activations during surprising when compared to correctly predicted trials over the inferior frontal gyrus (MNI [x,y,z]: 48, 24, 10 (BA 45) and 32, 24, −6 cluster sizes: 31 and 30). No significant activations were found for the opposite contrast (Exp > Sur).

Table 1
Summary of the ANOVA results for a 3 mm sphere ROI.

Main effect: RS (***)	$F(1,21)=27.11$	$p=0.00004$	$\eta p^2=0.56$
Main effect: expectation condition (**)	$F(2,42)=5.79$	$p=0.006$	$\eta p^2=0.22$
Main effect: hemisphere (***)	$F(1,21)=21.23$	$p=0.0002$	$\eta p^2=0.5$
Interaction: hemisphere × RS (*)	$F(1,21)=5.84$	$p=0.03$	$\eta p^2=0.22$
Interaction: hemisphere × RS × expectation condition (+)	$F(2,42)=2.95$	$p=0.06$	$\eta p^2=0.12$

To confirm that no region remained unnoticed by the commonly applied but rather rigorous FWE corrected threshold we also analyzed our data at a less conservative threshold ($p<0.0001_{uncorrected}$; cluster extent of >20 voxels). The Alt > Rep contrast and Sur > Exp showed some additional regions with significant activations (Table 2 and Fig. 4). Furthermore, when compared to surprising trials, correctly predicted ones (Exp > Sur) led to increased activation in the parahippocampal gyrus, hippocampus, claustrum and putamen (Table 2 and Fig. 4). The contrast testing differences between neutral and surprising conditions (Sur > Neu) revealed significant activations in the inferior and middle frontal gyri. Interestingly, these regions were also activated in the Sur > Exp contrast and in fact the location of the two regions is similar for both contrasts (Table 2 and Fig. 4). The whole-brain analysis did not reveal additional active clusters when testing for further expectation effects or for the interaction of RS with expectation conditions.

4. Discussion

Our major result is that surprising events lead to significantly larger activity as compared to unpredicted, neutral events, thereby supporting the hypothesis outlined on Fig. 1A and emphasizing the role of surprise in predictive coding processes.

Predictive coding models assume that ε relies on the discrepancy between observed and predicted sensory states (Friston, 2012), supporting the finding of surprise related enhancement of the activity. However according to theories of PC (Friston 2012) correct predictions reduce ε, pointing to the involvement of expectation suppression as well.

So far only a handful of studies tried to disentangle these mechanisms, surprise enhancement and expectation suppression, by the application of a third, neutral or unpredicted condition. Recently, Egner et al. (2010) tested subject's perceptual face expectation (low, medium and high) during a task that was orthogonal to the manipulation of expectations. Authors found that surprise events contributed more robustly (about twice as strongly) to FFA BOLD responses when compared to correctly predicted events. Unfortunately, Egner et al. (2010) did not report if their medium condition, where the cue signaled the occurrence of faces with 50% probability was different from either of the other two conditions or not. Our results confirm and extend these results, suggesting enhanced response during incorrectly predicted conditions, unlike the surprise minimization shown in choice behavior (Schwartenbeck et al., 2015).

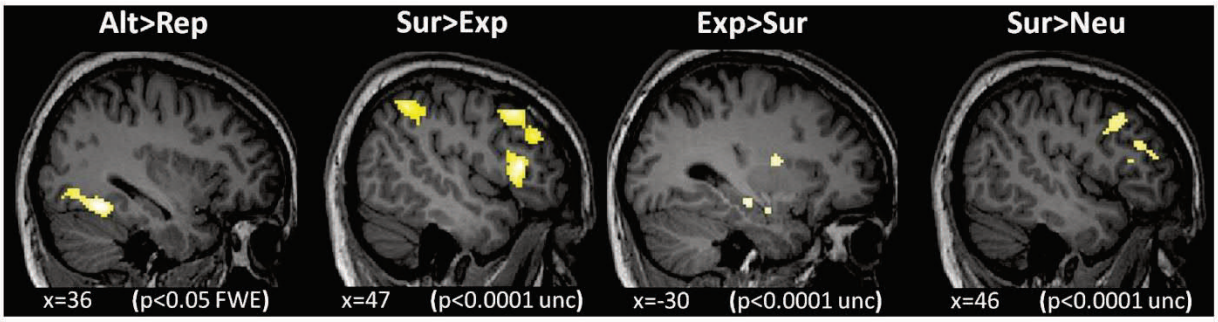

Fig. 4. Results of the whole-brain analysis. Significant activations for the main effects of trial (Alt > Rep) and for the main effects of expectation conditions (Sur > Exp; Exp > Sur and Sur > Neu) are presented (cluster extent of > 20 voxels).

Table 2
Summary of the significant activations based on the whole-brain analysis.

Contrast	Brain region	Coordinates	Cluster size	Threshold
Alt > Rep	Fusiform gyrus	36, −52, −14	351	(p < 0.05 FWE)
Alt > Rep	Middle occipital gyrus	−34,−78, 8	89	(p < 0.0001)
Sur > Exp	Brodmann area 45	48, 24, 10	31	(p < 0.05 FWE)
Sur > Exp	Inferior frontal gyrus	32, 24, −6	30	(p < 0.05 FWE)
Sur > Exp	Middle frontal gyrus	46, 20, 42	368	(p < 0.0001)
Sur > Exp	Middle frontal gyrus	40, 56, 2	149	(p < 0.0001)
Sur > Exp	Inferior frontal gyrus	−34, 20, −6	169	(p < 0.0001)
Sur > Exp	Inferior parietal lobe	50, −48, 48	290	(p < 0.0001)
Sur > Exp	Brodmann area 9	6, 38, 30	157	(p < 0.0001)
Exp > Sur	Parahippocampal gyrus	−34, −8, −20	59	(p < 0.0001)
	Hippocampus	−30, −20, −14		
Exp > Sur	Claustrum	−30, −2, 12	40	(p < 0.0001)
Exp > Sur	Putamen	32, −2, 6	21	(p < 0.0001)
Sur > Neu	Middle frontal gyrus	40, 8, 36	209	(p < 0.0001)
Sur > Neu	Inferior frontal gyrus	50, 24, 12	294	(p < 0.0001)
Sur > Neu	Inferior frontal gyrus	34, 26, −6	37	(p < 0.0001)

One important limitation of the current study is, however, that univariate BOLD signal analysis techniques are unable to exclude the role of ε unit activity reduction in determining lower responses in correctly as compared to non-predicted and incorrectly predicted trials. As the BOLD signal reflects the mixture of ε and representational unit activity, due to its low spatial resolution, we can not decide if the observed similar activity for the predicted and neutral, non-predicted conditions is due to similar ε activity within the two conditions or there is also an additional reduction of ε units be the correctly predicted events which is compensated by an enhanced representational unit activity, leading to similar response magnitude or the correctly predicted and non-predicted conditions.

Previously, Kok et al. (2012) found better multivariate pattern (MVPA) classification rates for expected conditions when compared to surprising conditions, suggesting that the reduction of the neural response amplitudes for expected stimuli is associated with an the improvement of the stimulus representation. Therefore, future MVPA studies could clarify further the neural mechanism behind this reduced BOLD response we observed for the non-predicted, neutral and predicted conditions as compared to unpredicted condition. If the classifier performance is equally higher for neutral and expected conditions, the observed expectation suppression is solely due to an increased ε unit activity in the unpredicted trials i.e. due to surprise. On other hand, if the classifier performance is lower for both surprising and neutral events, then one can assume that there is an additional ε unit activity reduction, driven by correct predictions.

Rahnev et al. (2011) also confirms this result when inducing expectations regarding the direction of a moving-dot pattern. Authors found a neural response enhancement for invalidly cued (therefore surprising) events when compared to expected and neutral events (with the expected cued activations falling in between the other two) in the dorsolateral prefrontal cortex and in the intraparietal sulcus. However, unlike in our study, the Rahnev et al. (2011) work revealed no expectation modulation in the sensory areas (in the motion-sensitive medial temporal cortex), but rather exclusively in the bilateral dorsolateral prefrontal cortex.

In contrast with our prior study (Grotheer and Kovács 2015) where a general reduction of the response was found for correctly when compared to incorrectly predicted trials, our current results could find such differences only for the alternating trials. However, this difference of results can easily be explained by the different experimental designs. First, due to the additional (neutral) expectation condition, in the current study, trials where expectations were fulfilled had an average probability of 50% over the 3 conditions only whereas in Grotheer and Kovács (2015) the same probability was 75%. Even though the ratio of Surprising/Expected trials was identical in the current and in the Grotheer and Kovács (2015) study, the overall number of trials in the expected and surprising conditions was significantly reduced. Second, the introduction of the neutral condition might also serve as distracter from the predictive conditions. PC assumes a constant re-estimation and update of predictions, yet subjects were aware of the equal probability occurrence of repetitions and alternations during the neutral conditions, thus it is possible that no predictions were formed during this specific condition, interrupting the constant up-dating and re-estimation of predictions. Indeed, predictable events usually occur in a non-random fashion, allowing the brain to infer about the probabilistic or deterministic regularity of the different events (Bubic and Schubotz, 2010). However, previous studies proposed that similar predictive strategies are employed to attempt the extraction of a pattern within random inputs as well (Schubotz and von Cramon, 2002). It should be noted that in the Schubotz and von Cramon (2002) study the involved task required participants to constantly indicate whether the last trials of a sequence were expected (correct) or surprising (violated) based on the sequence order, forcing the creation of predictive strategies during the randomized sequences. While in the current study the gender judgment task was orthogonal to the manipulation of expectation and the events were not presented sequentially (thus our participants were unable to use memory regarding previous

neutral events to infer about upcoming random events). Therefore, an overall reduction of the number of trials and the existence of the unpredicted trials might explain the absence of overall BOLD signal differences between E and S trials in the current study.

Contrary to what theories of predictive coding suggest (Arnal and Giraud, 2012) the neutral condition induced the lowest activity in our study, even showing a tendency for leading to lower activity than the correctly predicted condition. This result, however, has been observed in previous studies as well. Rahnev et al. (2011) found lower activations in the dorsolateral prefrontal and inferior parietal cortices for neutral when compared to predicted (incorrectly and correctly) trials. Two mechanisms are able to explain the higher FFA BOLD signal for correctly predicted when compared to unpredicted trials. First, it is possible that it reflects the activity of both representational and ε encoding units simultaneously. In this case, the lower ε can be compensated by the relatively larger representational unit activity during the correctly predicted trials, while only a small ε related activity and a relatively smaller representation unit activity exist in the neutral trials. Second, it is possible that correct predictions do not reduce ε to its minimum. Rather, ε remains larger even in an event that is predicted correctly. This ε, which is smaller in the unpredicted trials, could explain the larger BOLD signal for the correctly predicted trials. Testing these hypotheses, however, will require further specifically aimed studies, preferably with multivariate analysis techniques.

Expectation-based processes may be important in modulating repetition suppression (for a summary see Kovács and Vogels (2014) and Summerfield et al. (2008)). In the current study, we found significant RS for both the right and left FFA. The dependence of the RS on expectation condition, however, showed hemispheric differences: while the observed RS was independent of expectation condition over the left hemisphere it showed an interaction with expectations over the right hemisphere being the largest in the surprising condition. This suggests different neural mechanisms behind the RS for the two hemispheres. This would not be the first time such hemispheric differences are found. For example, Yovel et al. (2008) showed different neural mechanisms in the right and left FFA, finding that only the rFFA was sensitive to symmetry.

It is possible that enhanced responses for the surprising trials reflect the capture of attention additionally to the surprise effect originating from the violation of expectations. However the current experimental design did not enable us to test for possible attentional effects like previous studies: for instance, Jiang et al. (2013) manipulated expectation and attention effects orthogonally. Using multivariate pattern analysis, Jiang and colleagues show that attention enhances the precision of ε in FFA, due to an improvement of the stimulus representation in this area. Overall, the computation of fulfilled or violated expectations requires the attention of the observers (Larsson and Smith, 2012), meaning that attention is a precondition for discriminating expected from unexpected stimuli (for a summary of attention and prediction processes see the review by Summerfield and Egner (2009)).

The whole-brain analysis of the current study is congruent with Grotheer and Kovács (2015); in the sense that no expectation effects were revealed in early visual areas, unlike previous studies (Grotheer and Kovács, 2014; Larsson and Smith, 2012). This supports the idea that our experimental design, which induces expectations explicitly, produces expectation effects on higher-processing levels (Grotheer and Kovács, 2015). Furthermore, the similarity between active clusters for Surprise > Neutral and Surprise > Expected points once again to a distinction between surprising events from the other two (neutral and correctly predicted) conditions.

In summary, we observed elevated BOLD responses in the ventral visual stream for surprising events when compared to neutral ones, emphasizing the role of surprise in prediction based modulation of the BOLD signal. Crucially, the relationship of RS magnitude and expectation effect varies between hemispheres: being dependent in the right hemisphere and additive in the left hemisphere.

Conflict of interest

The authors declare no competing financial interests.

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3 Does surprise enhancement or repetition suppression explain visual mismatch negativity?

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Main research question:

Which neural mechanisms explain vMMN better: surprise related or repetition related responses?

EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

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COGNITIVE NEUROSCIENCE

Does surprise enhancement or repetition suppression explain visual mismatch negativity?

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Abstract

A long tradition of electrophysiological studies, using oddball sequences, showed that the neural responses to a given stimulus differ when their presentation occurs frequently (standards) as compared to rare, infrequent presentations (deviants). This difference, originally described in acoustic perception, can also be detected in the visual modality and is termed as visual mismatch negativity (vMMN). Also, a large number of studies detected the reduction of the neuronal response after the repetition of a given stimulus (repetition suppression – RS) and it was suggested that RS is the major mechanism of MMN, an explanation currently also supported by animal studies. However, human studies have proposed that a surprise-related response enhancement for the deviant stimuli might also underlie vMMN. Therefore, the aim of the current study was to disentangle which neural mechanism explains vMMN better: the surprise related response enhancement for the presentation of rare deviants or the RS related to the frequent presentation of the standards. Since the MMN depends strongly on the applied categories, we tested the neural mechanisms of vMMN for different stimulus categories (faces, chairs, real and false characters) using a visual oddball paradigm. We found significant vMMN for every stimulus category. Interestingly, the neural mechanisms behind vMMN were found to be category dependent (assuming no cross-adaptation effects): for faces and chairs it was largely driven by RS, whereas for real and false characters it was mainly due to surprise-related changes.

Introduction

Neural responses to rare and frequently repeated stimuli deviate from each other, as revealed by the mismatch negativity in event-related brain potentials (ERP) for both acoustic and visual stimuli (Czigler *et al.*, 2004). Visual MMN (vMMN) is considered as an indicator of the discrepancy between the automatic representation of environmental regularities and their violations (Cammann, 1990; Stefanics *et al.*, 2014).

Repetition suppression (RS – Henson, 2003 for review see Grill-Spector *et al.*, 2006) has been suggested to explain vMMN. RS describes the phenomenon of neuronal response attenuation after repeated events. It is the traditional explanation of (v)MMN (Näätänen *et al.*, 1978) and is also termed as stimulus-specific adaptation (for review see Baldeweg, 2006; Nelken & Ulanovsky, 2007) or refractoriness (Schröger, 1997; Heslenfeld, 2003; Kimura, 2012). More recently, however, vMMN has been considered as a manifestation of active memory representations (Stefanics *et al.*, 2014). According to models of predictive coding (PC – see Friston, 2005), the brain actively generates predictions of its sensory inputs, using a generative model (Friston, 2012). Consequently, through hierarchical memory representations, differences between predictions and the actual sensory input are computed and the (v)MMN would be a signal of these differences.

Typically, vMMN is identified in oddball paradigms, which consist of the presentation of a high probability (standard) stimulus intermixed with a low probability (deviant) stimulus. Recently, however, the so called "equiprobable" sequences (Jacobsen & Schröger, 2001; Jacobsen *et al.*, 2003) have been introduced to study vMMN (Kimura *et al.*, 2009). In these sequences, several stimuli are presented with the same probability as the deviants in common oddball sequences. It has been argued that the comparison of deviant responses embedded in the oddball and equiprobable conditions reveals a "genuine", surprise related (v)MMN (Czigler *et al.*, 2002; Astikainen *et al.*, 2008). However, despite the existence of this "genuine" vMMN, other studies still suggest the contribution of RS to MMN as well (Kimura *et al.*, 2009; Li *et al.*, 2012; Astikainen *et al.*, 2013). Additionally, multi-unit and local field potential recording studies of non-human primates failed to show a surprise related response to the violations of regularities (Farley *et al.*, 2010; Fishman & Steinschneider, 2012; Kaliukhovich & Vogels, 2014).

Here we tested the neural mechanisms of vMMN elicited by different visual stimulus categories by comparing conventional oddball and equiprobable sequences (Kaliukhovich & Vogels, 2014). Our

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aim was to separate the potential vMMN effects that are due to RS from those related to surprise. We reasoned that the vMMN would be due to RS if the standards of the oddball sequences are significantly different from the responses within the equiprobable condition while it would be rather due to surprise enhancement if the deviant responses are significantly different from those in the equiprobable condition (Kaliukhovich & Vogels, 2014).

Material and methods

Participants

Twenty-one healthy subjects (eight male; two left-handed, mean age (±SD): 23.5 (0.68) years) participated in the experiment after giving written, informed consent in accordance to the Declaration of Helsinki. The protocols were approved by the Ethical Committee of the Friedrich Schiller University Jena. No participant had a history of neurological or psychiatric illness and all had normal or corrected to normal vision.

Stimuli and procedure

Stimulus presentation was controlled via MATLAB R2014a (The Mathworks, Natick, MA, USA), using Psychtoolbox (Version 3.0.12). From a total 1842 grey-scale, digital photos of the 10 different stimulus categories, one image per category was randomly selected for each participant (396 full-frontal Caucasian adult faces (50% of female), similar to the face stimuli of Kovács *et al.* (2012, 2013) with mean luminance of 36.2 cd/m^2; 32 non-frontal chairs with mean luminance of 35.13 cd/m^2 – Kovács *et al.* (2013); 241 false characters (mean luminance: 11.90 cd/m^2); 281 real characters (mean luminance: 7.17 cd/m^2); 183 birds (mean luminance: 13.83 cd/m^2); 127 buildings (mean luminance: 23.84 cd/m^2); 91 cars (mean luminance: 17.06 cd/m^2); 32 fruits (mean luminance: 17.36 cd/m^2); 229 objects (mean luminance: 16.61 cd/m^2); 230 bodies (mean luminance: 26.27 cd/m^2)). Please note that altogether only 10 images were used in the experiment, however the images were different for each participant, as they were randomly selected from the above described, larger stimulus pool. Faces and chairs were placed behind a circular mask. Bird, chair, fruit, car, body and object images were collected from the public domain of the World Wide Web. Real and false characters were identical to those of the study by Grotheer & Kovács (2014). False characters were scrambled versions of the real characters (1–4 components of a particular letter were moved randomly to a different position in a way similar to Grotheer & Kovács (2014). The stimuli were centered on a uniform grey background (17.11 cd/m^2) and presented using a 19" CRT monitor (60 Hz refresh rate) from a 90 cm viewing distance. Stimulus size was 3° in radius. A chin rest was used to diminish head movements during data recording.

The experimental design was similar to what has previously been used to evaluate the presence of genuine surprise related responses to deviants in visual oddball sequences (Kaliukhovich & Vogels, 2014). Four stimulus categories were used (faces, chairs, real and false characters) based on prior neuroimaging results testing the effect of statistical probability on RS (faces: Grotheer *et al.*, 2014; Kovács *et al.*, 2012, 2013; Larsson & Smith, 2012; chairs: Kovács *et al.*, 2013; real and false characters: Grotheer & Kovács, 2014). The stimulus categories were arranged into two pairs (1. Faces vs. Chairs; 2. Real vs. False Characters) that were then used in the oddball sequences.

The stimuli were shown with specific stimulus presentation probabilities under five experimental conditions. Five blocks of 100 trials were administered per experimental condition, resulting in a total of 25 blocks and in approximately 45 min total recording time. The order of the blocks was counterbalanced across subjects. Two consecutive blocks were never taken from the same experimental condition. Two of the five experimental conditions are typical oddball sequences, where the two stimuli from a pair, for example *face1* and *chair1*, are randomly interleaved and displayed with probabilities of 0.9 and 0.1, respectively (Fig. 1). In the other two conditions the stimulus probability was reversed; following the given example that is, *face1* and *chair1* were shown with probabilities of 0.1 and 0.9, respectively. Therefore, both stimuli of a given category-pair were presented frequently (hereby designated to as a standard) as well as rarely (deviant). The number of consecutive standards was pseudo randomized between 2 and 5. In the fifth condition, the same stimuli that were presented in the oddball sequences (e.g. *face1, chair1, character1* and *falsecharacter1*) were interleaved randomly with six other stimuli from six different categories (birds, bodies, buildings, cars, fruits, and objects). In this condition the probability of each ten stimulus category was identical (i.e. 0.1). The face, chair, real and false character stimuli when presented in this "equiprobable" condition are further referred to as a control. In total, there were five possible experimental conditions: four oddball sequences (two reversed oddball sequences – one for each category pair) and one equiprobable sequence. Stimuli were presented for 350 ms each, separated by a random inter-trial interval (varied between 500 and 700 ms in 50 ms steps). The different sequences were separated by 1s pause interval.

To ensure that subjects were attending the stimuli, a simple reaction time task was applied. The target was a red cross (16.4 cd/m^2) with a shorter (0.13°) and a longer (0.3°) arm. The cross was continuously presented at the centre of the screen and its configuration was randomly changed in every 5–15 trials in a way that the position of the shorter and longer arms was exchanged. Participants were instructed to detect these changes and to reply as quickly (with a maximum response time-window of 1050 ms) and correctly as possible.

ERP recording

The electroencephalographic (EEG) signal was recorded with sintered Ag/AgCl electrodes using a 64-channel Biosemi Active II system (Biosemi, Amsterdam, The Nerderlands). The electrodes were arranged according to the extended 10/20 system at the scalp positions Fp1, FT9, AF3, F1, F3, F5, F7, FT7, TP9, FC3, FC1, C1, C3, C5, T7, TP7, PO9, CP3, CP1, P1, P3, O9, P7, P9, PO7, PO3, O1, Iz, Oz, POz, Pz, CPz, Fpz, Fp2, FT10, AF4, Afz, Fz, F2, F4, F6, F8, FT8, TP10, FC4, FC2, FCz, Cz, C2, C4, C6, T8, TP8, PO10, CP4, CP2, P2, P4, O10, P8, P10, PO8, PO4 and O2. Note that the Biosemi system uses a combined ground/reference (CMS/DRL) circuit (cf. to http://www.biosemi.com/faq/cms&drl.htm). The data was digitally transformed to an average reference using EEGLAB (Delorme & Makeig, 2004), a signal processing toolbox for MATLAB. Horizontal electro-oculograms were recorded from the outer canthi of the eyes, while vertical electro-oculograms were monitored bipolarly from electrodes above and below the left eye. The signal was digitalized at a 512 Hz sampling rate (bandwidth: DC to 120 Hz) and filtered off-line with: 1. a 12 dB/octave Butterworth high pass-filter with a cut-off frequency of 0.1 Hz to remove DC drifts; 2. a digital 25 Hz 24 dB/octave low-pass filter, using ERPLAB (Lopez-Calderon & Luck, 2014). The EEG was

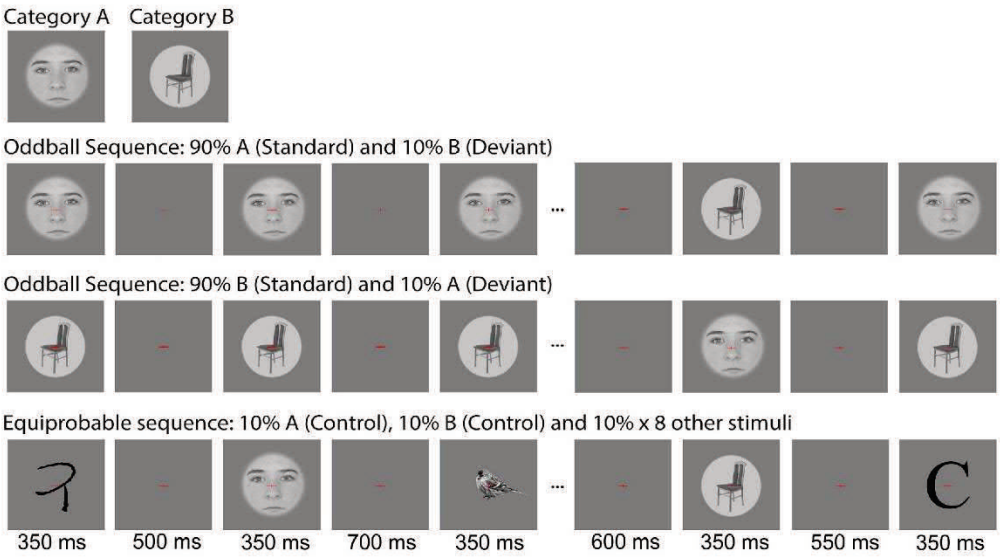

FIG. 1. Experimental design and conditions. Two images (A and B) were selected and displayed in oddball and reversed oddball sequences for each category pair (i.e. Faces vs Chairs and Characters vs False Characters), where each stimulus was presented either frequently (probability 0.9, standard) or rarely (probability 0.1, deviant). In addition, there was an equiprobable sequence with 10 different stimuli (including the 4 stimuli used in the oddball sequences and 6 other stimuli from various categories) presented with the same probability (0.1).

segmented off-line into 950 ms long epochs (100 ms pre-stimulus interval). Trials containing an amplitude change exceeding ±70 μV on any channel were rejected (this criterion was applied to all trial types and electrodes including the electro-oculogram recording ones). On average 21% of all the non-target trials were used for further analysis (the average trial amount for the different stimulus conditions was 322, 36 and 36 for all standards, deviant and control, respectively. Note that the number of trials was similar for the four probe-stimulus categories). The epochs were averaged for each stimulus condition (standard, deviant and control), stimulus category, recording channel and participant separately. Note that all standard stimuli were included in the final analysis. To identify change-related activities, the ERPs evoked by standard stimuli in the oddball sequences were subtracted from the ERPs elicited by the deviant stimuli in the reversed oddball sequences (Deviant-*minus*-Standard). The same procedure was used to evaluate differences between control and standard stimuli (Control-*minus*-Standard), testing for repetition related response reductions, as well as for the differences between deviants and controls (Deviant-*minus*-Control), testing for surprise related response enhancements. Note that only physically identical stimuli, i.e. from the same category were compared in the role of deviant, standard and control conditions, meaning that the described comparisons are performed separately for the four stimulus categories.

Analysis and comparisons

To characterize the time-course of the vMMN objectively, we performed a point-by-point *t*-test (criterion: a cluster of at least two neighboring electrodes with a minimum of 20 consecutive data points, i.e. corresponding to a 40 ms time segment with a significant ($P < 0.01$) difference) in a series of pair-wise comparisons between the different stimulus conditions (i.e. Deviant vs. Standard, Control vs. Standard and Deviant vs. Control) for each subjects separately (Thorpe *et al.*, 1996). We carried out this analysis over the lateral and posterior recording channels (TP9, T7, TP7, PO9, CP3, CP1, P1, P3, O9, P7, P9, PO7, PO3, O1, Oz, POz, Pz, CPz, TP10, T8, TP8, PO10, CP4, CP2, P2, P4, O10, P8, P10, PO8, PO4 and O2), typically reflecting functions of the temporal and occipital visual cortexes (Sams *et al.*, 1997). While, prior MMN studies typically analyzed only certain, pre-defined time windows over a few electrodes, in the current study we included the entire ERP curve to test the category specificity of the vMMN in detail and in a hypothesis-free manner. Time by electrode statistical plots are used to present the results of this analysis, in which significant differences between the relevant conditions are color-coded as a function of the amplitude differences (Jacques *et al.*, 2007).

In this analysis a negative value at a certain time-point for the deviant-standard comparison indicates for example that the standard leads to a more negative voltage value than the deviant (Stand > Dev), while a positive value indicates that the deviant leads to a more positive value than the standard (Dev > Stand).

To determine the portion of the conventional vMMN that is due to repetition suppression or surprise enhancement, we calculated the percentage of significant difference present in the statistical plots of the conventional vMMN for the Control-Stand and Dev-Control conditions for each category separately. For this we considered the significant differences present in the statistical plots of the conventional vMMN as 100% and calculated the percentage of significant MMN time points which were overlapping with the Control-Stand (RS) and with the Dev-Control (surprise or "genuine" vMMN) conditions separately. Additionally, to quantify the dependence of the conventional vMMN on these effects, we correlated the wave differences of the different effects (Dev-Stand, Control-Stand and Dev-Control) with each other for each category separately. Note that the correlations of conventional MMN with Control-Stand and with Dev-Control were only performed for the time-windows in which the conventional vMMN could also be explained by RS or surprise

(genuine vMMN) or in other words, when the conventional vMMN was overlapping with RS (Control-Stand) or with surprise effects (Dev-Control).

An additional analysis was performed to evaluate how RS develops over time for the different categories. For this analysis, instead of including every standard stimuli in the calculation only the last standard of a row was included. As the number of standards varied from 2 to 9 in a row, only those with more than 3 standard trials were included in this analysis. This way, we could balance the number of standard (41) and deviant (36) stimuli better.

Results

Behavior

Participants needed on average 661 ms (±SD = 103 ms) to detect the configuration change of the central cross with an average accuracy of 77% (±SD = 24%) and there was no difference in accuracy between experimental conditions ($F_{4,80} = 1.26$, $P = 0.29$, $\eta p^2 = 0.06$). However, reaction times were significantly lower for the oddball and reversed oddball sequences of the real and false characters pair when compared to faces and chairs oddball and reversed oddball sequences as well as compared to the equiprobable sequence ($F_{4,80} = 14.38$, $P < 1e\text{-}6$, $\eta p^2 = 0.42$): equiprobable (Fisher LSD *post hoc* test: $P < 1e{-}5$), oddball (Fisher LSD *post hoc* test: $P < 0.001$); reversed oddball (Fisher LSD *post hoc* test: $P < 0.01$). This difference might be explained by the fact that the characters were black, while the other stimulus types included different greyscale values as well. Furthermore, the reaction times of the equiprobable conditions were significantly longer when compared to the reversed oddball condition of the faces vs chairs stimulus pair (Fisher LSD *post hoc* test: $P = 0.04$).

ERP data

Event-related potentials

All stimuli elicited a large positive component in the 95–135 ms time window (P1) with a peak occurring at around 115 ms (Fig. 2). Other components such as the N1/N170 and the P2 could also be identified on the ERPs (Fig. 2). We observed that differences in amplitude between the standard, deviant and control were time and category dependent. Also, it was possible to detect strong differences between the deviant and standard conditions for all the four categories suggesting the existence of conventional vMMN in our paradigm for every stimulus category.

Conventional vMMN (Deviant-Standard)

We observed significant deviant-standard differences within the 139–650 ms and 377–623 ms time-windows for faces and chairs, respectively (Fig. 3). The analysis of these difference waves for faces revealed that ERPs are more negative for the deviants when compared to the standards. Note, however that a few channels showed a positive amplitude difference (CP3, CP1, CP2 and CPz) within the 139–300 ms time-window, which is due to a more positive signal for deviants when compared to standards. Yet within the 350–600 ms time-window 11 electrodes show an opposite direction, positive vMMN for faces. For chairs the deviants elicited elevated responses when compared to standards within the same time-windows.

False and real characters also showed a significant vMMN but within slightly different time-windows, between 156–787 ms and 147–630 ms, respectively (Fig. 4). Both real and false characters exhibited a combination of positive and negative amplitude differences. Specifically, negative vMMN amplitudes dominated the earlier while positive amplitude differences were more pronounced in

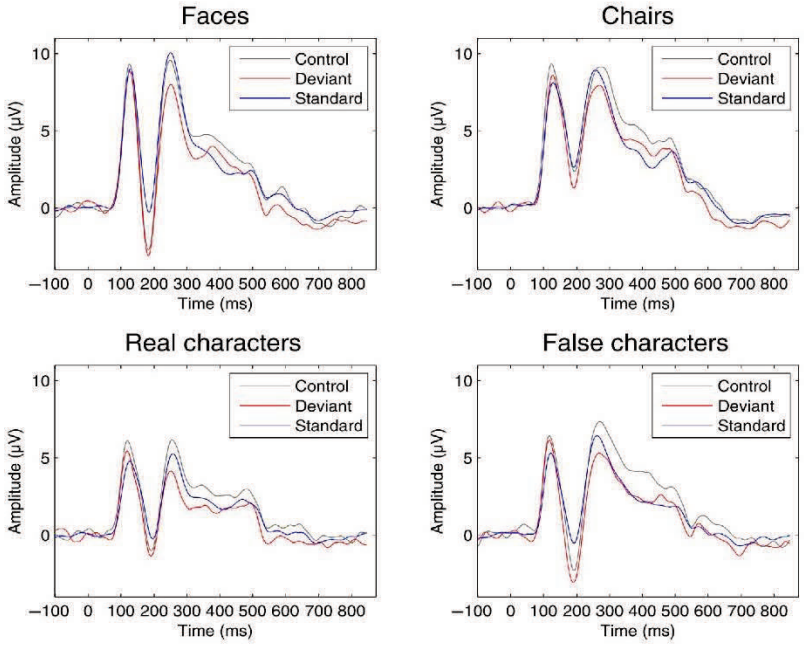

FIG. 2. Group average event-related potentials at PO8 electrode plotted from −100 to 850 ms for standard, deviant and control conditions of the 4 probe-stimuli categories.

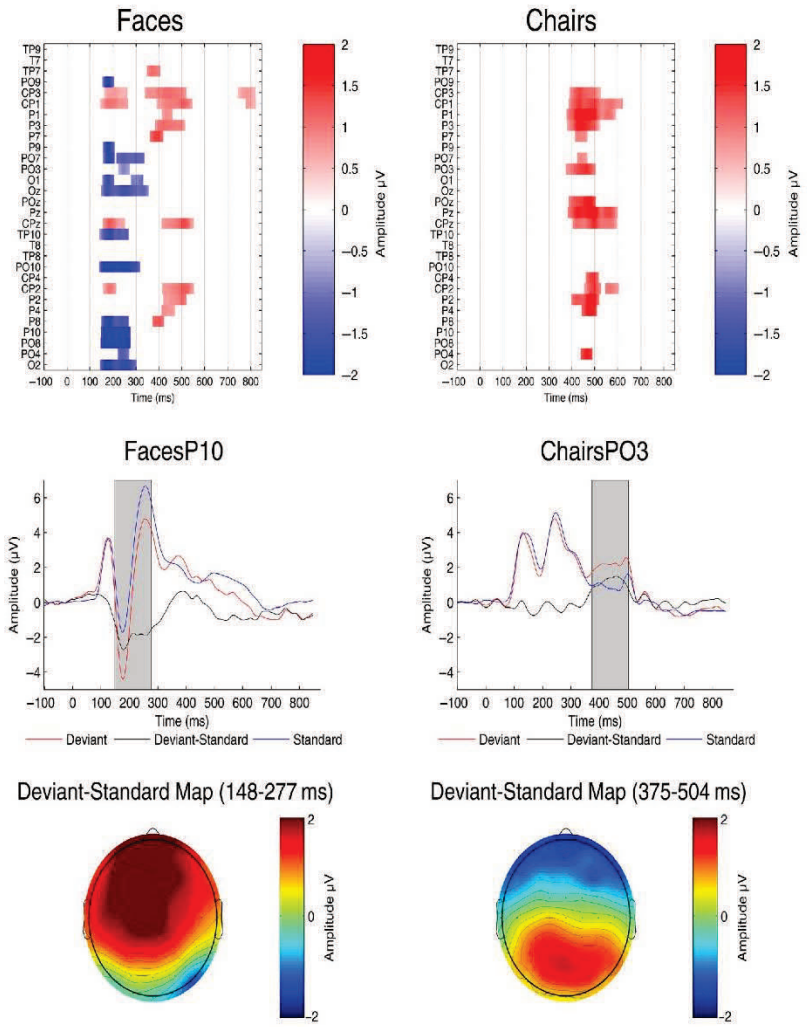

FIG. 3. Conventional vMMN – Differences between deviant and standard stimuli for faces (left) and chairs (right). Top: time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference). Bottom: representative ERPs at channel P8 and PO3 electrodes with the highlighted (grey region) significant differences between stimulus conditions for faces and chairs respectively.

the later time-window (Fig. 4). Importantly, electrodes that showed a positive vMMN in the later phase did not show a negative vMMN in the early phase and vice-versa. Essentially, the same results were obtained when using only the last standards for the comparisons. Please note that in this case only the last of a continuous row of standard stimuli was chosen for the analysis, meaning that 41 standard stimuli were compared to the 36 deviant stimuli. The only difference between the results of this and the conventional analysis when every standard stimulus was included was that for false characters no significant conventional vMMN effect was observed for the former case.

Suppression (Control-Standard)

We observed significant differences associated with repetition related response suppression (RS) between the control and the standard conditions for every stimulus category (Figs 5 and 6). Significant RS was found for faces between 146 to 848 ms; for chairs between 111–556 ms; for real characters from 365 to 440 ms and for false characters between 92–555 ms.

Importantly, the earliest RS effect for faces had a similar time-window to the amplitude difference observed for the conventional vMMN effects, i.e. for the differences between deviants and standards. This suggests that the early vMMN effect, for faces is mainly driven by RS. It is essential to note that almost all the electrodes (P8, PO8, P10, O2, PO10, TP10, Oz, O1, PO7, P9, PO9, CP1 and CPz) that showed a significant RS effect, also showed a significant vMMN effect within the same time-window. Moreover, the scalp distribution presented of the Dev-Stand (Fig. 3) and the Control-Stand (Fig. 5) comparisons are very similar for faces at around 200 ms, suggesting further that the conventional vMMN for faces is due to RS effects.

Similarly, the RS obtained for chairs can also explain the observed vMMN effects of the PO3, P4, POz, PO4, P1, P3 and P7 electrodes. Regarding the character stimuli, we observed that the conventional vMMN effects can only be explained by RS at a few

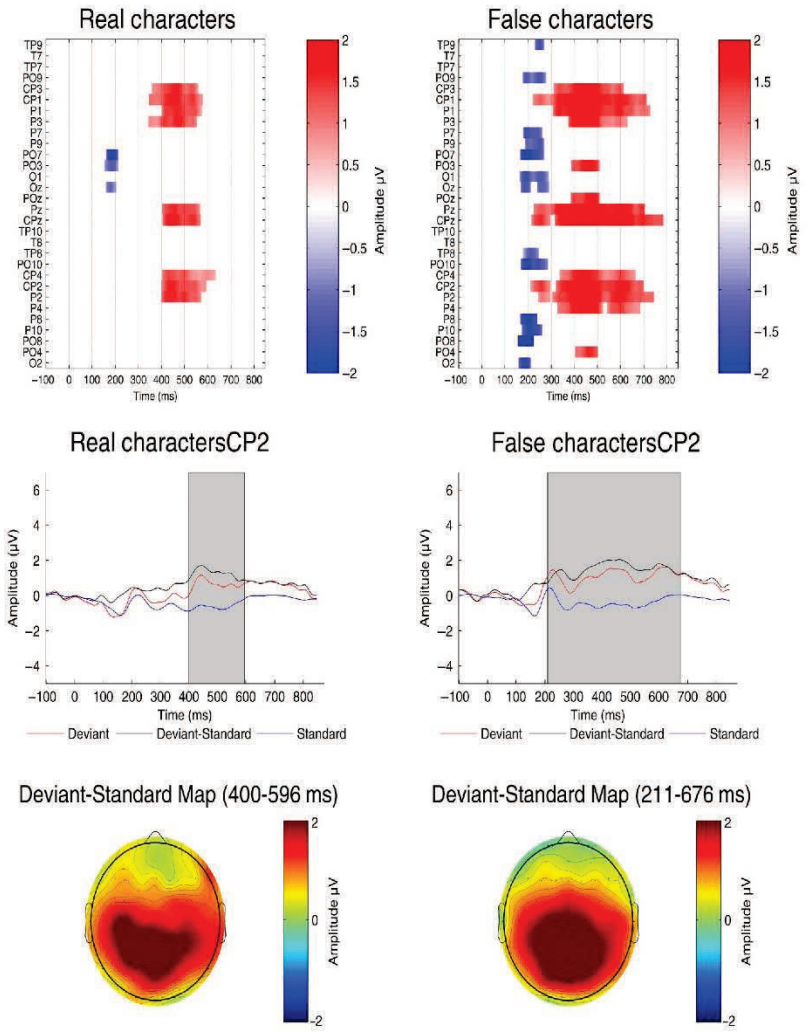

FIG. 4. Conventional vMMN – Differences between deviant and standard stimuli for real (left) and false (right) characters. Top: time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference). Bottom: representative ERPs at channel P3 and P1 electrodes with the highlighted (grey region) significant differences between stimulus conditions for real and false characters respectively.

electrodes (Fig. 6) and therefore no example ERP is presented here on Fig. 6.

When the last standards (i.e. only the last standard of a row was chosen for analysis, resulting in the inclusion of 41 standards, where 41 is similar to the number of deviants – 36) were analysed the results were similar except for false characters that did not show any significant effect.

Surprise enhancement (Deviant-Control)

We only found significant deviant-control differences for chairs (see Fig. 7) and for characters in the form of positive and negative differences within the 362–717 ms and the 207–655 ms time-windows for real and false characters, respectively (Fig. 8).

Crucially, the majority of the significant electrodes sites and time-ranges with positive amplitude differences of the deviant vs control comparison (Fig. 8) are comparable to the conventional vMMN effects (Fig. 4) for real and false characters. This suggests that most of the vMMN effects for characters can be explained by a surprise related response enhancement for the deviant stimuli, in other words a genuine vMMN.

Relations of vMMN with RS and surprise

The detailed comparison of the conventional vMMN with the RS and surprise related differences revealed that more than 40% of the vMMN effects can be explained by RS for faces and chairs (Table 1) and the correlation of these two effects is strong and significant. Note that the percentage refers to the amount of significant conventional MMN (i.e. the difference between Stand and Dev) time points which are overlapping with the Control-Stand (RS) or with the Dev-Control (surprise or "genuine" vMMN) conditions. On

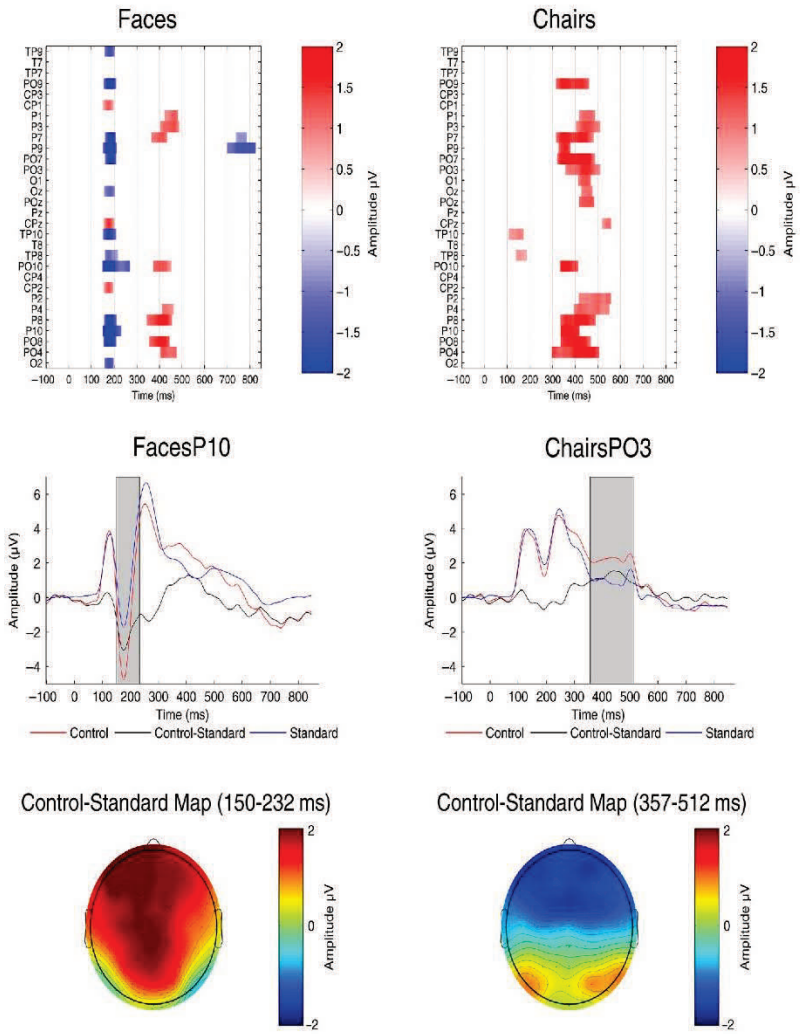

FIG. 5. Repetition Suppression – Differences between control and standard stimuli for faces (left) and chairs (right). Top: time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference). Bottom: representative ERPs at channel P8 and PO3 electrodes with the highlighted (grey region) significant differences between stimulus conditions for faces and chairs respectively.

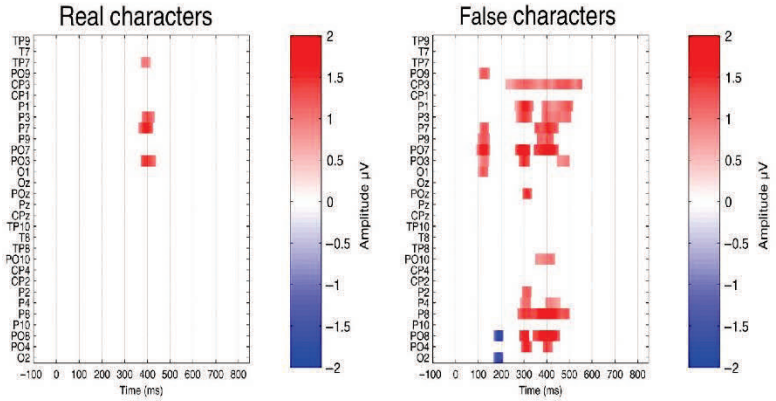

FIG. 6. Repetition Suppression – Differences between control and standard stimuli for real (left) and false (right) characters. Time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference).

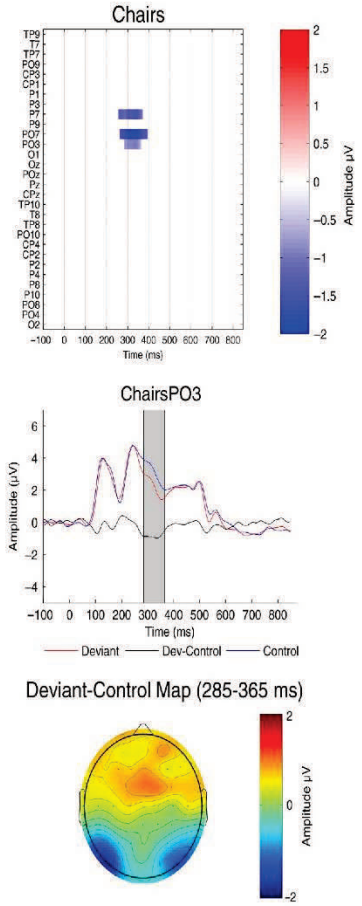

FIG. 7. Surprise Effect – Differences between deviant and control stimuli for chairs. Top: time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference) for chairs. Bottom: representative ERPs at channel PO7 electrode with the highlighted (grey region) significant differences between stimulus conditions.

other hand, the vMMN that was observed for character stimuli overlapped more with surprise effects (Table 1). In addition, the vMMN of real characters also overlapped with some RS related effects. However, the correlation of the conventional vMMN with RS was not significant. Interestingly, false characters showed high correlation between RS and surprise effects as well.

Overall, the separate analysis of the last standard stimuli revealed the same results with exception of false characters (for which no vMMN was observed).

Altogether, these results support further the conclusion that while the conventional vMMN for faces and chairs is mostly due to RS, it is dominantly due to surprise for real and false characters, emphasizing the category specificity of the effect.

Discussion

We found that the neural mechanisms that underlie the conventionally observed vMMN effects are stimulus category dependent. While vMMN is driven by repetition related RS for faces and chairs, it is mostly due to surprise-related response enhancement for real and false characters.

Previous (v)MMN studies using equiprobable control conditions, similar to the one of the present study have already suggested that the differences between deviant and standard stimuli are based on stimulus-specific adaptation processes (for review see Khouri & Nelken, 2015). Kaliukhovich & Vogels (2014) suggested that the inferior temporal cortex of the macaques boost activity to the deviants without a surprise related response for different stimulus categories, including faces. Similarly, our results show the complete lack of surprise related response in the conventional vMMN for faces and chairs. Furthermore, the neural contribution of repetition related RS to vMMN was present, althought to a different degree, for every stimulus category. This is in agreement with previous studies which revealed that the vMMN effects elicited by facial expressions are based on stimulus-specific adaptation (Li *et al.*, 2012; Astikainen *et al.*, 2013). Unfortunately, Kaliukhovich & Vogels (2014) did not test for differences between the different stimulus categories, presenting only their results for the average of different categories. In the auditory domain, however, other animal studies showed no surprise related response to the violations of regularities in either rats (Farley *et al.*, 2010) or monkeys (Fishman & Steinschneider, 2012).

In humans, Kimura *et al.* (2009) presented bars with different visual angles to test for vMMN. They found that the vMMN, driven by surprise enhancements, appeared only within the 200–250 ms time-window while an earlier effect was driven by RS. This points to the involvement of two distinct neural mechanisms in vMMN: repetition and surprise related responses, acting within different time-windows. This conclusion is in agreement with our findings for real and false characters, where we found the contribution of the two mechanisms similarly. It is worth noting that, the character stimuli of the current study (simple, high-contrast shapes) are more similar to the 2D black bars used by Kimura *et al.* (2009) than to greyscale images of chairs and faces, which are more complex and are also commonly associated with a third dimension (Todd, 2004). Thus, the possibility that the dimensional representation nature or stimulus complexity influences vMMN should not be excluded.

Previously, Czigler *et al.* (2002) and Astikainen *et al.* (2008) could show genuine vMMN, i.e. surprise related response differences. The stimuli used in these two studies were simple geometric forms (colored vs. black vertical square-wave gratings – Czigler *et al.*, 2002; bars with changing orientation – Astikainen *et al.*, 2008). However, Kimura *et al.* (2009) also used bars with different orientations as stimuli and in addition to the genuine vMMN also found RS related differences. It is important to note, however, that the Czigler *et al.* (2002) and Astikainen *et al.* (2008) studies analyzed differences between the deviant and control conditions only. In other words no analysis was performed to exclude repetition related RS effects by calculating the difference between control and standard, which might therefore have also explained some vMMN effects in those studies.

Interestingly, our results indicate that the vMMN for real and false characters is mainly explained by surprise related differences. A recent study (Sulykos *et al.*, 2015) also tested vMMN effects in an oddball paradigm for a familiar (N) and an unfamiliar letter (И; the mirrored version of the familiar ones). The results from this study indicate that vMMN is sensitive to the familiarity in a way that the peak latency of vMMN is higher for the familiar letter, contrary to what we have found for real and false characters. Importantly, the compared latencies between the two stimulus types were only at 140 ms and 130 ms for familiar and unfamiliar stimuli in the same study, respectively. Furthermore it is visible on the Fig. 1 of the Sulykos *et al.* (2015) study that the amplitude differences between deviants and standards are higher for the unfamiliar as

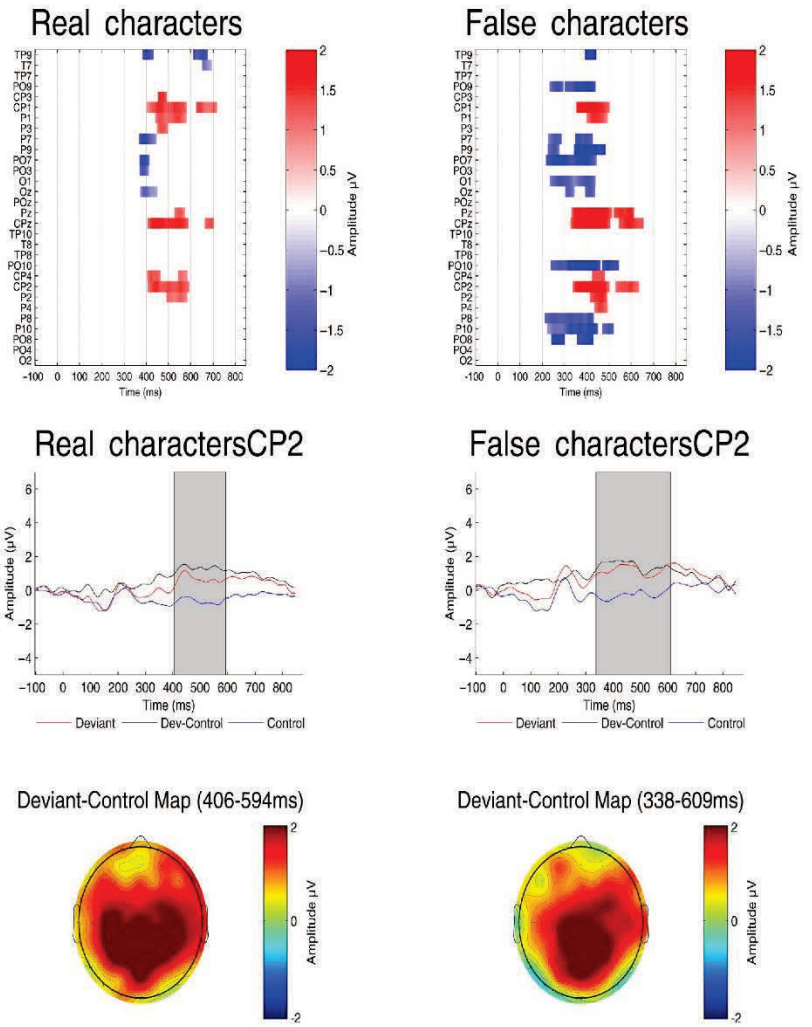

FIG. 8. Surprise Effect – Differences between deviant and control stimuli for real (left) and false (left) characters. Top: time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference). Bottom: representative ERPs at channel P3 and P1 electrodes with the highlighted (grey region) significant differences between stimulus conditions for real and false characters respectively.

TABLE 1. Percentages and correlations of vMMN with RS and surprise

	Comparison	Faces, %	Chairs, %	Real characters, %	False characters, %
All standards	MMN & RS	41.03 (R = 0.9; P = 0.01)	51.36 (R = 0.89; P = 0.02)	2.31 (R = 0.16; P = 0.39)	15.97 (R = 0.9; P = 1e−3)
	MMN & Surprise	0	0	42.44 (R = 0.87; P = 7e−7)	24.61 (R = 0.82; P = 3e−6)
Last standards	MMN & RS	31.08 (R = 0.93; P = 1e−5)	41.18 (R = 0.77; P = 0.15)	2.55 (R = 0.11; P = 0.6)	0
	MMN & Surprise	0	0	47.62 (R = 0.88; P = 6e−5)	0

compared to the familiar stimuli within the 200–300 ms and within 500–600 ms. Nevertheless, our results point to an overall larger vMMN effect for false as compared to real characters, even for earlier time-windows. The difference between this and prior studies might be explained however by the different tasks and paradigms. In the current study participant's task was to detect changes in a centrally presented red cross and the stimuli were presented centrally behind the cross. Sulykos *et al.* (2015) divided the screen into two halfs with an upper part (where the attention of the participants was directed by a video game) and a lower part (where multiple stimuli were displayed). Therefore such differences in visual stimulation and attentional demands can explain the different results.

It is well-known that stimulus luminance affects ERP waves. In addition, drastic luminance changes were also directly related to attentional modulations (Wijers *et al.*, 1997). Although the current experiment includes inherent differences of luminance, due to the different stimulus category sets, the performed analysis only compared ERP waves that were obtained for the same stimulus

categories. Therefore luminance differences are unlikely to affect our results. Yet, it is also possible that luminance differences between the character and other stimulus categories might have induced a surprise effect in the control, equiprobable blocks. However, if that was the case there would have been a similar response for the deviant and control conditions, leading to no differences between them. In other words, assuming that the same surprise based mechanisms are activated in the deviant and the control conditions there should be no or only a small difference between these two conditions. However, as our results show very strong differences between deviants and control for both character types, the role of different luminance of the stimuli for the control condition can be excluded.

There are a few experimental constrains related to our paradigm. One is related to the reduced number of trials for the deviant and control conditions, driven by the low probability (10%) of presentation of these conditions, the existence of four stimulus categories and of the target trials which are not used in the final analysis. Second, a cross-adaptation between different elements of the equiprobable sequence can theoretically also occur. This study assumes that there is no such cross-adaptation and therefore the performed comparisons are useful to identify the mechanisms behind vMMN. Yet, if there is some cross-adaptation the results might be explained by the sharpness of the neural tuning for the different stimulus categories (Li *et al.*, 1993; Wiggs & Martin, 1998).

Further, vMMN experiments ideally should include a control for attentional processing of the background stimuli to determine how much attention remains to process the stimuli and to verify that vMMN occurs pre-attentively or unintentionally (Sulykos *et al.*, 2015). Yet, the vast majority of the vMMN experiments adopt a target task, similarly to the one of the current study (e.g. Stefanics *et al.*, 2011).

Importantly, vMMN studies usually show late, parietal, positive effects (LPPs) which may reflect other processes, connected to attentional shifting or updating (for review see Morlet & Fischer, 2014).

It is possible that the overall early vMMN and RS effects for faces are related to the early face-sensitivity of the electrophysiological response (Linkenkaer-Hansen *et al.*, 1998; Itier & Taylor, 2002) and to a stronger N170 component for faces as compared to other stimulus categories (Bentin *et al.*, 1996; Carmel & Bentin, 2002). The relationship of the face sensitive N170, its category specific adaptation (Kovács *et al.*, 2006) and the face sensitivity of the currently observed RS in oddball paradigms will require further studies.

In conclusion, we observed that different stimulus categories lead to vMMN, but the underlying neural mechanisms are different: repetition related RS for faces and chairs, whereas surprise-related changes are more dominant for real and false characters.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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Abbreviations

EEG, electroencephalography; ERP, event-related potential; fMRI, functional magnetic resonance imaging; PC, predictive coding; RS, repetition suppression; vMMN, visual mismatch negativity.

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4. Visual mismatch negativity and fMRI signal adaptation correlate in the occipital-temporal cortex

This section is a slightly adapted version of the manuscript written by Prof. Dr. Gyula Kovács and me, that has been submitted to Neuroimage.

Main research question:

What is the relation between the electrophysiological measured vMMN and the signal adaptation in the neuroimaging experiments (fMRIa) within a typical and widely used oddball paradigm?

Abstract

Several electrophysiological studies found response differences to a given stimulus when it is repeated frequently as compared to when it occurs rarely in oddball sequences. Initially defined in acoustic perception, such difference also exists in the visual modality and is referred to as visual mismatch negativity (vMMN). However, the repetition of a stimulus also leads to the reduction of the blood oxygen-level dependent (BOLD) signal (fMRI adaptation, fMRIa) when compared to alternating stimuli in fMRI experiments. So far no study compared the vMMN to fMRIa within the same paradigm and participants. Here we tested the possible connection between fMRIa and vMMN in a visual oddball paradigm in two separate sessions, acquiring electrophysiological and neuroimaging data for real and false characters from the same participants. We found significant vMMN as well as fMRIa for both character types. Importantly, the magnitude of the vMMN over the CP1 electrode cluster showed a significant correlation with the fMRIa within the letter form area, for real characters. This finding suggests that similar neural mechanisms are responsible for the two phenomena.

Keywords: vMMN, characters, fMRI, surprise, EEG

1. Introduction

The exposure to rare (Deviant) stimuli among frequently repeated (Standard) ones within an oddball paradigm elicits a discrepancy between the neural activity associated with the Deviant and Standard stimuli. This phenomenon is termed as mismatch negativity (MMN) and has been found for both the acoustic and the visual domains in event-related brain potential (ERP) studies (Czigler et al., 2004). While there are several available theories explaining visual MMN (vMMN), current results suggest that it is an automatic representational difference elicited by the violations of regularities, established in an environment (Stefanics et al., 2014).

The most recent explanation for (v)MMN relies on the influential theory of predictive coding (PC, Friston, 2005). PC theories describe the brain as a multi-level hierarchical cascade of processing units, where the generated predictions are compared to the actual sensory inputs at each level. The differences between the predictions and the inputs are computed by hierarchical memory representations and only this "error" signal is transferred further to higher-level cortical areas in the hierarchy, optimizing the energy usage of the brain. Taking into account that (v)MMN can be considered as a manifestation of active memory (Kremláček et al., 2016; Stefanics et al., 2014), it has been suggested that it corresponds to the signal difference of the frequent, thereby predicted and the rare, therefore surprising stimuli. Accordingly, (v)MMN reflects the magnitude of the estimated prediction error.

Dominantly, (v)MMN is tested by electrophysiological methods, due to the high variability of its effects within short temporal windows, i.e. the (v)MMN effects are neither stable nor equal during the whole post-stimulus time-window (see Amado & Kovács, 2016). So far only a few auditory studies have used neuroimaging methods to

better understand the neural background of MMN by the superior spatial resolution of fMRI (Gomot et al., 2006; Leff et al., 2009; Molholm et al., 2005; for a review on auditory pitch studies of MMN see Deouell, 2007). Briefly, the findings of the these studies are related to the atypicalities of autism spectrum disorders (Gomot et al., 2006), to the vowel-specific mismatches (Leff et al., 2009) and to the dependence of MMN on various auditory features (Molholm et al., 2005). Two studies applied both electrophysiological and neuroimaging methods to investigate MMN effects (Hedge et al., 2015; Liebenthal et al., 2003). Liebenthal et al., (2003) tested the effect of sound frequency on MMN. The results of this study revealed a correlation of the activity within the superior temporal gyrus and the right superior temporal plane with the magnitude of the electrophysiologically measured MMN.

In a more recent vMMN study, single and double bars were used as stimulus combinations in oddball paradigms (Hedge et al., 2015): in one combination the single bars were the Standards and the double bars were the Deviants, while the opposite arrangement was used for the other combination. The EEG results indicated clear vMMN only for the single bar-Standard/double bar-Deviant condition, while the fMRI results showed that frontal areas underlie change-detection. Thus, applying both fMRI and EEG techniques with an oddball paradigm can lead to detailed information about the neural mechanisms, involved in the detection of environmental differences.

It is worth mentioning that the two above referred studies applied only whole-brain fMRI analysis with (Liebenthal et al., 2003) or without (Hedge et al., 2015) correlating it to the ERP data. To the best of our knowledge, so far no study used the superior sensitivity of a region of interest (ROI)-based analysis technique to measure fMRIa in specifically targeted brain regions and to evaluate its relation to the electrophysiologically measured (v)MMN. This is surprising, as it is known that the

category-specific areas of the human occipital-temporal cortex are sensitive to stimulus repetitions (Weigelt et al., 2011) and show fMRIa for repeated when compared to alternating stimuli (Malach, 2012). For example, both the face sensitive fusiform face area (FFA) as well as the character sensitive letter form area (LFA) show fMRIa (characters - Grotheer & Kovács, 2014; faces - Henson, 2003). Furthermore, fMRIa is also a commonly applied technique to investigate repetition related neural phenomena generally (Weigelt et al., 2011).

Importantly, different theories can be used to explain the differential responses obtained for standards and deviants in an oddball paradigm. Certain theories explain (v)MMN responses as a result of adaptation effects related to the repetitions of the standards (Kaliukhovich & Vogels, 2014), while others explain the (v)MMN responses as a genuine surprise related enhancement for the rare stimuli (Winkler, 2007). There are also studies suggesting the involvement of both effects (i.e. surprise and adaptation) in the creation of the vMMN response (Barto et al, 2013; Stefanics et al, 2014). Furthermore, the neural mechanisms of fMRIa are still under debate: the role of neural adaptation in defining the measured BOLD signal reduction is not clear (for reviews see e.g. Kar & Krekelberg, 2016; Larsson & Smith, 2012).

Both, fMRIa and (v)MMN have recently been both connected to theories of PC as well (Auksztulewicz & Friston, 2016; Grotheer & Kovács, 2014; Kremláček et al., 2016). Despite these facts, it is not clear whether the electrophysiologically measured (v)MMN, obtained in oddball paradigms and the fMRIa of neuroimaging experiments that is usually obtained by blocks or pairs of stimuli are explained by similar neural mechanisms or not. Here, we reasoned that if both the electrophysiologically observed (v)MMN and the fMRIa of neuroimaging studies are related to the same neural functions, for example by the Bayesian mechanisms of predictive coding, then there

should be a strong correlation between them.

The aim of the current study is to test whether the mechanisms measured by electrophysiological and neuroimaging methods are analogous for oddball paradigms. In other words, to investigate how does fMRIa, usually expressed by a stimulus repetition related response reduction of the occipital-temporal cortex in neuroimaging experiments, relates to the commonly observed vMMN. We chose roman and false roman characters as stimuli for the following reasons: we could previously demonstrate that (1) there is a strong fMRIa for these stimuli within the recently described LFA (Grotheer & Kovács, 2014), (2) vMMN can be elicited for these stimuli (Amado & Kovács, 2016) and finally (3) the neural mechanisms of the fMRIa appear to be different for real and false characters in the sense that it can be explained by PC theories for only the highly practiced roman, real characters, while it appears to be insensitive to top-down predictive effects for the novel false characters (Grotheer & Kovács, 2014a).

Briefly anticipating our results, we found significant vMMN for both real and false characters electrophysiologically, supporting our previous findings (Amado & Kovács, 2016) as well as an fMRIa. Importantly, there appears to be a correlation between the magnitude of vMMN and the fMRIa for the real characters in the letter form area and left lateral occipital cortex.

2. Material and methods

2.1 Participants

18 healthy volunteers participated in the experiment after giving written, informed consent in accordance to the Declaration of Helsinki. The protocols were approved by the Ethical Committee of the Friedrich Schiller University Jena. No participant had a history of neurological or psychiatric illness and all had normal or corrected to normal vision. One participant was excluded from the final analysis due to excessive artifacts in the EEG data, which contaminated >50% of the trials. Thus, 17 subjects (7 male; 2 left-handed, mean age (±SD): 23.4 (0.8) years) were included in the final analysis.

2.2 Stimuli and Procedure

Stimuli were delivered using MATLAB R2014a (The Mathworks, Natick, MA, USA), via Psychtoolbox (Version 3.0.12). One image per category was chosen randomly for each participant from a total pool of 93 grey-scale, digital photos of the 10 different stimulus categories (18 false Roman characters; 18 real Roman characters; 7 Cyrillic characters; 10 Georgian characters; 6 Arabic script; 9 Chinese script; 8 Zodiac symbols; 7 Mathematical symbols; 6 common Currency symbols; 4 Card symbols). Altogether only 10 stimuli were used in the experiment, however these were randomly selected from the above described stimulus pool for each participant. Real roman and novel false characters were identical to those of the studies by Grotheer & Kovács (2014) and by Amado & Kovács (2016). False characters were the scrambled versions of the real characters (1-4 components of a particular letter were moved randomly to a different position, in a way identical to Grotheer & Kovács, 2014). The other

characters (Georgian and Cyrillic), symbols (mathematic, zodiac, card and currency) and scripts (Chinese and Arabic) were collected from the public domain of the World Wide Web and matched in contrast and size to the real characters. The stimuli (mean luminance: 9.78 cd/ m^2) were centered on a uniform grey background (17.11 cd/m^2) and presented using a 19" CRT monitor (60Hz refresh rate) from a 90 cm viewing distance for the electrophysiological session. For the fMRI sessions, the stimuli were back-projected via an MRI-compatible LCD video projector (NEC GT 1150, NEC Deutschland GmbH, Ismaning, Germany) onto a translucent oval screen, placed inside the scanner bore. Stimulus size was 3° in radius in both cases. A chin rest was used to diminish head movements during electrophysiological data recording, while a foam padding or vacuum cushion was placed between the head and the MRI coil in the fMRI session.

The experimental design was similar to what has previously been used to separate the presence of genuine surprise related responses to Deviants from the suppression of the response to the standards in visual oddball sequences (Kaliukhovich & Vogels, 2014; Amado & Kovács, 2016). Briefly, two stimulus categories were used (real Roman characters and their false character versions) based on prior neuroimaging and electrophysiological studies testing the effect of statistical probability on fMRIa (Grotheer & Kovács, 2014) as well as vMMN (Amado & Kovács, 2016). Importantly, both stimulus categories are known to induce neuronal activations in the letter form area (LFA, Thesen et al., 2012) and in the lateral occipital cortex (LO, Malach et al., 1995).

The two probe stimuli were presented with different probabilities under three experimental conditions. Three sequences of 100 trials were administered for each experimental condition (see below), resulting in a total of 9 sequences and in

approximately 45 minute recording time. These sequences of 100 trials were divided into 10 shorter blocks each, resulting in a block length of 10 trials. This procedure was similar to the previous fMRI studies of MMN (Hedge et al., 2015; Molholm et al., 2005; Opitz, Mecklinger, Von Cramon, & Kruggel, 1999) and is necessary as conventional event-related MMN designs must use such short ISIs (see Näätänen et al., 2004 and Sams et al., 1993 to evaluate how increased ISIs affect the MMN response) which make the separation of the BOLD signal for subsequent stimuli impossible.

The order of the sequences was counterbalanced across subjects with the restriction that two consecutive sequences could never come from to the same experimental condition. The three experimental conditions were the following: two oddball sequences (a normal and a reversed oddball) and a control, equiprobable sequence. Specifically, in the normal oddball sequence the two stimuli of a pair, for example *real_character1* and *false_character1*, were randomly interleaved and displayed with probabilities of 0.9 and 0.1, respectively (Fig.E4.1). In the other, reversed-oddball, sequence the stimulus probabilities were reversed (i.e. *real_character1* and *false_character1* were presented with probabilities of 0.1 and 0.9, respectively). Therefore, both stimuli of a stimulus-pair were presented frequently (hereby designated to as Standards) as well as rarely (Deviants). The number of successive Standards was pseudo randomized between 4 and 14 within a sequence. In the third condition, the same stimuli that were presented in the oddball and reversed oddball sequences (e.g. *character1* and *falsecharacter1*) were interleaved with eight other stimuli from the other eight categories (Cyrillic and Georgian characters; Arabic and Chinese script; Zodiac, Mathematical, Currency and Card symbols), randomly with equal probabilities (i.e. 0.1 each). This “equiprobable” or control condition is identical to that of Amado & Kovács, (2016) and Kaliukhovich & Vogels,(2014) and enables the

detailed analysis of the electrophysiologically measured MMN. The comparison of the equiprobable to the Deviant condition reveals genuine surprise-related differences while its comparison to the Standards lets one estimate stimulus-specific adaptation processses (Barto, Mirolli, & Baldassarre, 2013; Kaliukhovich & Vogels, 2014; see supplementary material).

Stimuli were presented for 350 ms each, separated by an inter-trial interval of 450 ms. The different blocks were separated by 4s intervals of the presentation of a grey screen. Note that for the fMRI session the full experiment was divided into three runs, but the overall structure of the sequences, block and trials was the same for the EEG and fMRI recordings. The control (equiprobable) as well as the oddball and reversed oddball sequences were administered in separate blocks. The oddball sequences were divided into two different types of blocks: one type contained only Standards (False_Characters_St, Real_Characters_St), while the other one was composed of Standards and Deviants as well (Real_Characters_Dev, False_Characters_Dev).

To guarantee that participants attended the stimuli, a simple reaction time task was applied, similar to that of Amado & Kovács, (2016). Briefly, the target was a red cross (16.4 cd/m^2) with a shorter (0.13°) and a longer (0.3°) arm located at the center of the screen during the entire experiment and its configuration changed randomly in every 5th – 15th trial; in a way that the location of the shorter and longer arms was exchanged. Participants were instructed to detect these changes and to respond as fast (with a maximum response time-window of 800 ms) and accurately as possible.

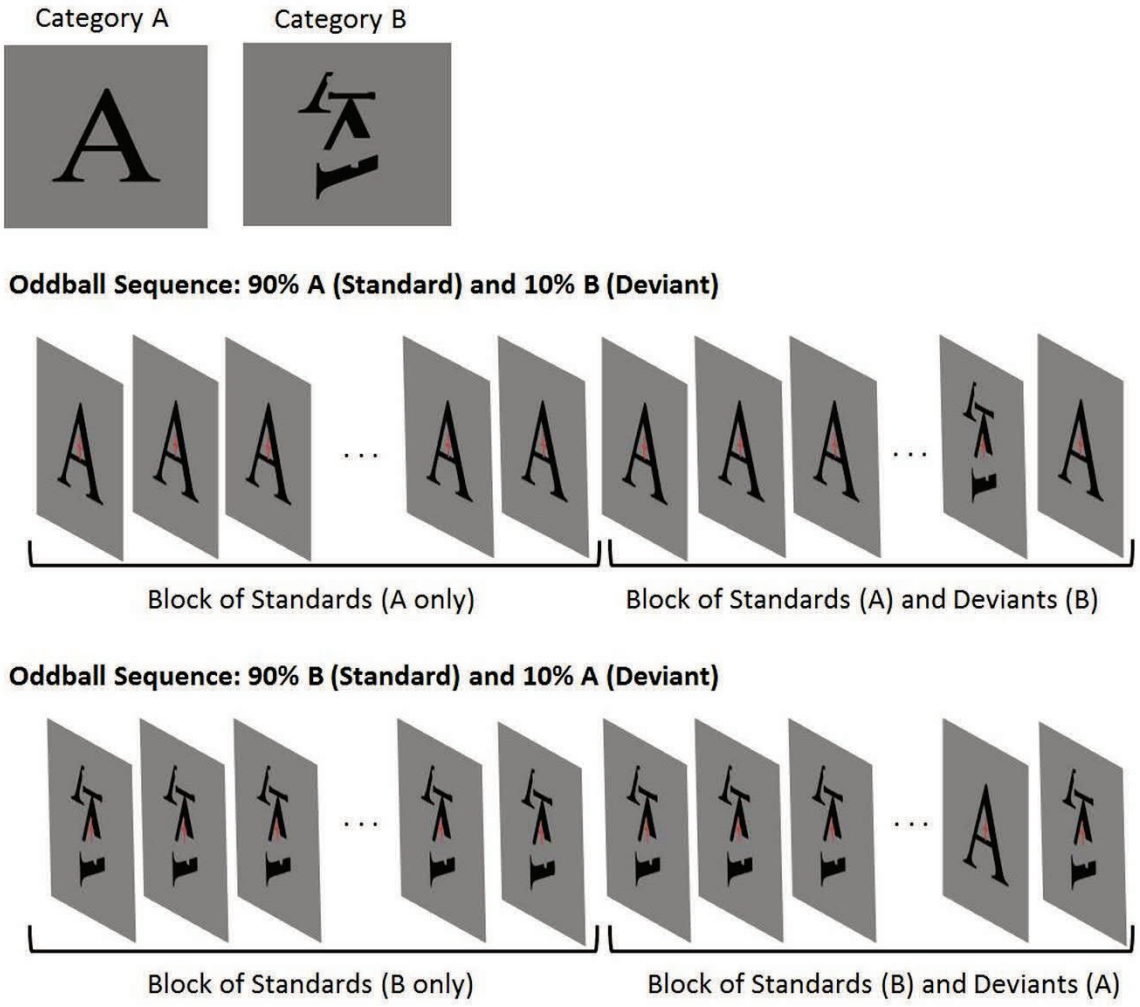

Figure E4.1 - Experimental design and oddball conditions. Two images from the two categories (A – real character and B – false character) were selected and displayed in oddball and reversed oddball sequences, where each stimulus was presented either frequently (probability 0.9, standard) or rarely (probability 0.1, deviant). Please note the two block types in each oddball sequence.

2.3 ERP Recording

The electroencephalographic (EEG) data was acquired with sintered Ag/AgCl electrodes using a 64-channel Biosemi Active II system (Biosemi, Amsterdam, The Nerderlands). The electrodes arrangement corresponds to the extended 10/20 system. Note that the Biosemi system uses a combination between ground and reference (CMS/DRL) circuits (cf. to http://www.biosemi.com/faq/cms&drl.htm). The EEG signal was digitally converted to an average reference using EEGLAB (Delorme & Makeig, 2004), a signal processing toolbox for MATLAB. Vertical electro-oculograms were recorded bipolarly from electrodes above and below the left eye, while horizontal electro-oculograms were recorded from the outer canthi of the eyes. The signal was digitalized at a 512 Hz sampling rate (bandwidth: DC to 120 Hz) and filtered off-line with: 1. a 12 dB/octave Butterworth high pass-filter with a cut-off frequency of 0.1 Hz to remove DC drifts; 2. a digital 25 Hz 24 dB/octave low-pass filter, using ERPLAB (Lopez-Calderon & Luck, 2014). The EEG was segmented off-line into 1000ms long epochs (200ms pre-stimulus interval). Trials with an amplitude range exceeding ±70 μV on any channel were discarded (this principle was applied to all trial types and electrodes including the electro-oculogram recording ones). On average 78% of the non-target trials were used for further analysis (the average trial amount for the different stimulus conditions was 209, 23 and 24 for all Standards, Deviants and Controls, respectively. Note that the number of trials was similar for the two probe-stimulus categories). The epochs were averaged for each stimulus condition (Standard, Deviant and Control), stimulus category, recording channel and participant, separately. Note that all Standard stimuli were included in the final analysis. To identify change-related activities, the ERPs evoked by Standard stimuli in the oddball

sequences were subtracted from the ERPs elicited by the Deviant stimuli in the reversed oddball sequences (Deviant-*minus*-Standard). Note that only physically identical stimuli, i.e. from the same category were compared as Deviants and Standards, meaning that the described comparisons are performed separately for the two stimulus categories.

2.4 ERP Analysis and Comparisons

To characterize the time-course of the vMMN objectively, we performed a point-by-point t-test (similar to that of Amado & Kovács, 2016). Briefly, to judge the Deviant-Standard difference as significant a cluster of at least two neighboring electrodes had to reach the significance level of $P<0.01$ for 20 consecutive data points i.e. a minimum time of 40ms (Thorpe et al., 1996). We carried out this analysis over the lateral and posterior recording channels (TP9, T7, TP7, PO9, CP3, CP1, P1, P3, O9, P7, P9, PO7, PO3, O1, Oz, POz, Pz, CPz, TP10, T8, TP8, PO10, CP4, CP2, P2, P4, O10, P8, P10, PO8, PO4 and O2), which reflect the functions of the temporal and occipital visual cortexes (Sams et al., 1997). In the current study, we included the entire ERP curve to test the vMMN effects in detail and in a hypothesis-free manner, following the procedure of Amado & Kovács (2016). Time by electrode statistical plots are used to present the results of this analysis, in which significant differences between the relevant conditions are color-coded as a function of the amplitude differences (Jacques et al., 2007).

2.5 Imaging Parameters and Data Analysis

Imaging was done with a 3-Tesla MR scanner (Siemens MAGNETOM Prisma fit, Erlangen, Germany). T2* weighted images were collected using an EPI sequence (35 slices, 10° tilted relative to axial, TR =2000 ms; TE = 30 ms; flip angle = 90°; 64 x 64 matrices; 3mm isotropic voxel size). A high-resolution T1-weighted, 3D anatomical image was acquired using a MP-RAGE sequence (TR = 2300 ms; TE = 3.03 ms; 192 slices; 1 mm isotropic voxel size).

Details of preprocessing and statistical analysis were described previously (Cziraki, Greenlee, & Kovács, 2010). Briefly, the functional images were realigned, normalized to the MNI-152 space, resampled to 2 x 2 x 2 mm resolution and spatially smoothed with a Gaussian kernel of 8 mm FWHM (SPM12, Statistical Parametrical Mapping, Welcome Department of Imaging Neuroscience, London, UK). A separate functional localizer run (640 sec long, 20 sec epochs of real characters, false characters, objects and Fourier randomized versions of characters, interleaved with 10 sec of blank periods, 2 Hz stimulus repetition rate; 300 ms exposure; 200 ms blank) served as basis for Regions of Interest (ROIs) detection. ROI creation was performed with MARSBAR 0.44 toolbox for SPM (Brett, Johnsrude, & Owen, 2002). The location of the LFA was determined individually, as an area responding more intensely to real as compared to false characters and Fourier randomized versions of characters ($p<0.0001_{UNCORRECTED}$; Thompson et al., 2016; Grotheer & Kovács, 2014a; Puce et al., 1996). Its location could be identified in 15 participants [average MNI coordinates (±SE): -41 (2), -57 (3), -17 (1); average cluster size (±SE): 30 (1) voxels]. The LO was determined individually as an area responding more intensely to objects than to Fourier noise

($p<0.0001_{UNCORRECTED}$). Its location could be identified bilaterally in 15 participants. Yet, the analysis was performed separately for the right (rLO) and the left (lLO) LO, due to hemispherical asymmetries (Nakamura et al., 2005) and possible hemispheric differences in character processing (Papçun, Krashen, Terbeek, Remington, & Harshman, 1974). Thus, the rLO could be identified in 17 participants, while the lLO could be found in 15 participants [average MNI coordinates (±SE): 47 (1), -75 (2), -5 (1) and -41 (3), -79 (2), -2 (1); average cluster size (±SE): 28 (2) and 30 (2) voxels, for right and left hemispheres, respectively].

A time series of the mean voxel value within the areas of interest was calculated and extracted from our event-related sessions using custom made scripts and Marsbar. The convolution of each of the 5 experimental blocks (Real_Characters_St, Real_Character_Dev, False_Characters_St, False_Characters_Dev, Control) with the canonical hemodynamic response function (HRF) of SPM12 (SPM12, Welcome Department of Imaging Neuroscience, London, UK) was used to define predictors for a General Linear Model (GLM) analysis of the data. While the Control blocks were modelled in the fMRI experiments as well, due to the applied block-design, it is not usable to separate the surprise and adaptation related neural mechanisms of MMN. This is because a Control block contains ten different stimulus types (see above), which is known to elicit larger BOLD responses than the oddball sequences where only two stimulus types are used. Therefore, we modelled, but ignored the Control condition in the present analysis of the neuroimaging data (for the analysis of the Control electrophysiological data kindly see supplementary material). We performed repeated measures ANOVAs for the LO and LFA activity separately with category (2, Real Character and False) and experimental condition (2, Standard and Deviant) as factors. Post-hoc analyses were executed using Fisher LSD tests.

2.6 Correlation between in EEG and fMRI data

To test whether the response difference of Standards and Deviants is related between the electrophysiological and neuroimaging data, a correlation analysis was performed between the two data sets. For the electrophysiologically measured vMMN, four groups of electrode clusters and two time-windows were selected, on the basis of the current and prior results (Amado & Kovács, 2016). As our prior results (Amado & Kovács, 2016), as well as the current data suggested the dominance of the posterior electrodes in vMMN we restricted our analysis to the 32 electrodes in or posterior to the midline. The selection of the electrophysiological data was done using the following criteria: a minimum of 100ms time sequence of significant vMMN in at least 3 neighboring electrodes had to be significant. In sequences longer than 100ms, the most dominant vMMN time component with a duration of 100ms in a sequence was correlated to the fMRI results. The thereby defined electrode clusters and time-windows are marked by black boxes on Figure E4.3a. The vMMN differences were computed for these time-windows and for each electrode cluster separately. The two time-windows corresponded to an early (200ms to 250ms) and a late (400ms to 500ms) period where both, the current and previous studies (Amado & Kovács, 2016) have found significant vMMN effects for several electrodes in a cluster. The four electrode clusters were the following. The CP1 cluster included CP1, CP3, P1 and P3; the Pz cluster included the Pz, CPz and POz; the CP2 cluster was composed of CP2, CP4, P2 and P4 and finally the PO8 electrode cluster included PO8, P10 and P8. Note that the early time-window was only analyzed for the PO8 cluster, while the late time-window was calculated for the other three clusters. This selection was based on the time windows and clusters that showed the most robust conventional vMMN effects

in the statistical plots (Fig. E4.3). The voltage differences between Deviants and Standards were averaged for each cluster. For the fMRI data, the peak of the BOLD response was used to calculate the difference between Deviants and Standards for each area and participant separately. Finally, the difference between Deviant and Standard conditions was correlated for the EEG and fMRI data-sets across participants, for each ROI and electrode cluster separately.

3. Results

3.1 EEG

3.1.1 Behavior

Participants detected the configuration change of the central cross with an average accuracy of 80% (± SEM 5%) and needed on average 563ms (± SEM 16ms). No significant results were found for these measures across conditions.

3.1.2 Event-related potentials

Both real and false characters elicited a large positive component within the 95 to 135 ms time window (P1) with a peak occurring at around 115 ms (Fig. E4.2). Other ERP components such as the P2 and the N1/N170 could also be identified (Fig. E4.2).

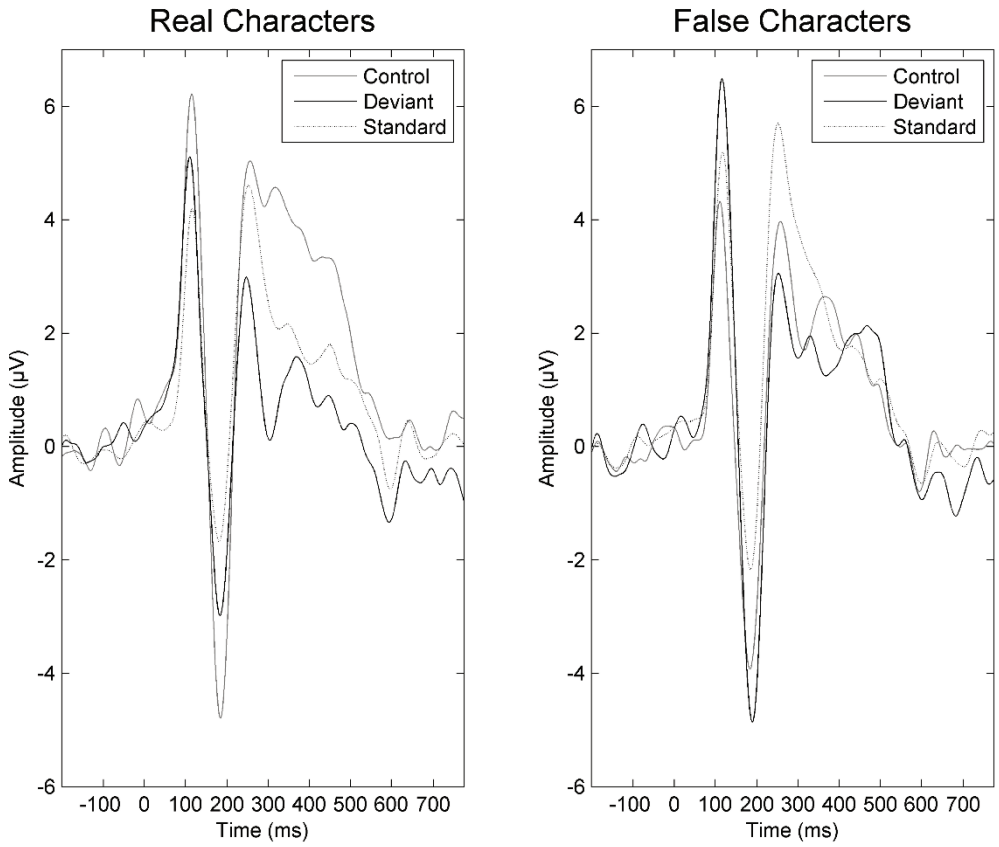

Figure E4.2- Grand averages of the ERPs at the PO8 electrode, plotted from -200 to 800ms for Standard, Deviant and Control conditions for the two probe-stimulus categories separately.

3.1.3. vMMN (Deviant-Standard)

We observed significant Deviant-Standard differences within the 166-800 ms and 160-800 ms time-windows for real and false characters, respectively (Fig.E4.3). Interestingly, the time by electrode statistical plots are very similar for real and false characters.

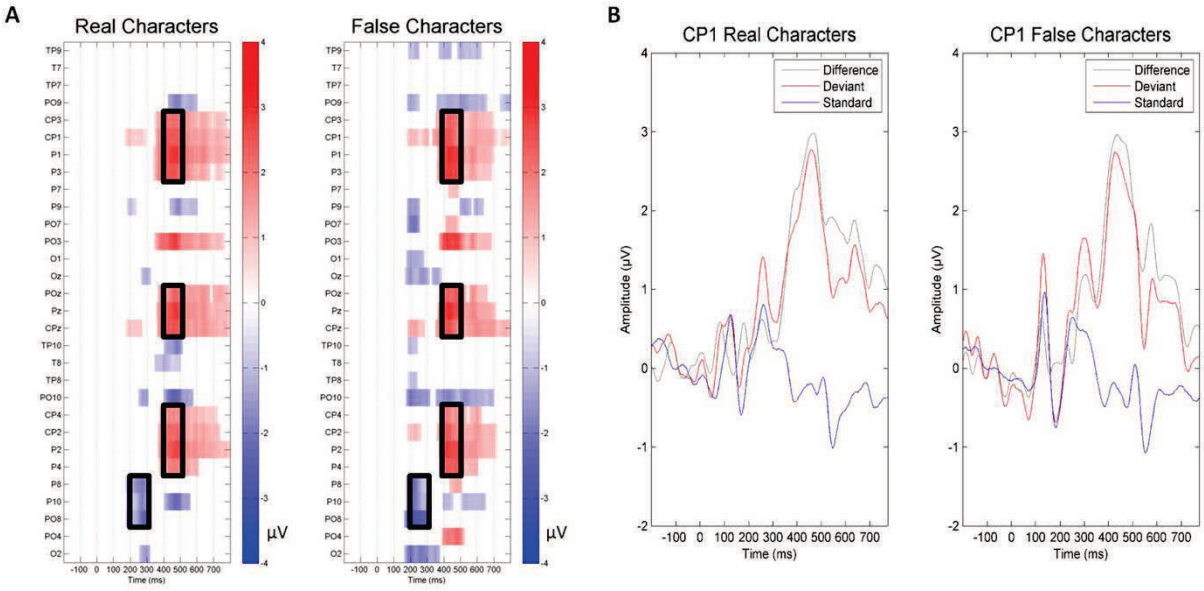

Figure E4.3 – Conventional vMMN – A. Differences between Deviant and Standard stimuli for real characters (left) and false characters (right) plotted in time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference). Black boxes indicate the clusters and time-windows, used for the subsequent correlation analysis (for further details see the section 2.6 of the Material and Methods) B. Example of the CP1 difference potential responses to both real (left) and false characters (right) of Deviant and Standard stimuli as well as the difference between Deviant and Standard.

3.2 fMRI

3.2.1 Behavior

Participants detected the configuration change of the central cross with an average accuracy of 77% (± SEM 5%) and needed on average 636ms (± SEM 17ms). No significant results were found for these measures across conditions.

3.2.2 Letter Form Area

We observed significantly lower BOLD response for Standard as compared to Deviant blocks i.e. fMRIa (Fig.E4.4A main effect experimental condition: $F(1,50)=7.4$, $p=0.009$) with an average signal difference of 0.13% (equivalent to a relative signal difference of 18%). We also found a trend for a main effect of character type ($F(1,50)=3.32$, $p=0.07$), which was due to a larger BOLD response for real when compared to false characters, supporting previous results (Grotheer & Kovács, 2014a). Furthermore, we found no significant interaction between experimental condition and character type.

3.2.3 Lateral Occipital Cortex

We also observed significant fMRIa in both right and left LO (Fig.E4.4B and Fig.E4.4C; main effect of experimental condition in right and left LO, respectively: $F(1,50)=7.4$, $p=0.009$ and $F(1,44)=8.5$, $p=0.007$) with an average signal difference of 0.13% and 0.15% (equivalent to a relative signal difference of 18% and 21%, respectively). Interestingly and similar to LFA, there was a strong trend for a main effect character type in the left LO ($F(1,50)=3.32$, $p=0.07$), suggesting a larger BOLD response for real compared to false characters. Moreover, no significant interaction was found between character type and experimental condition.

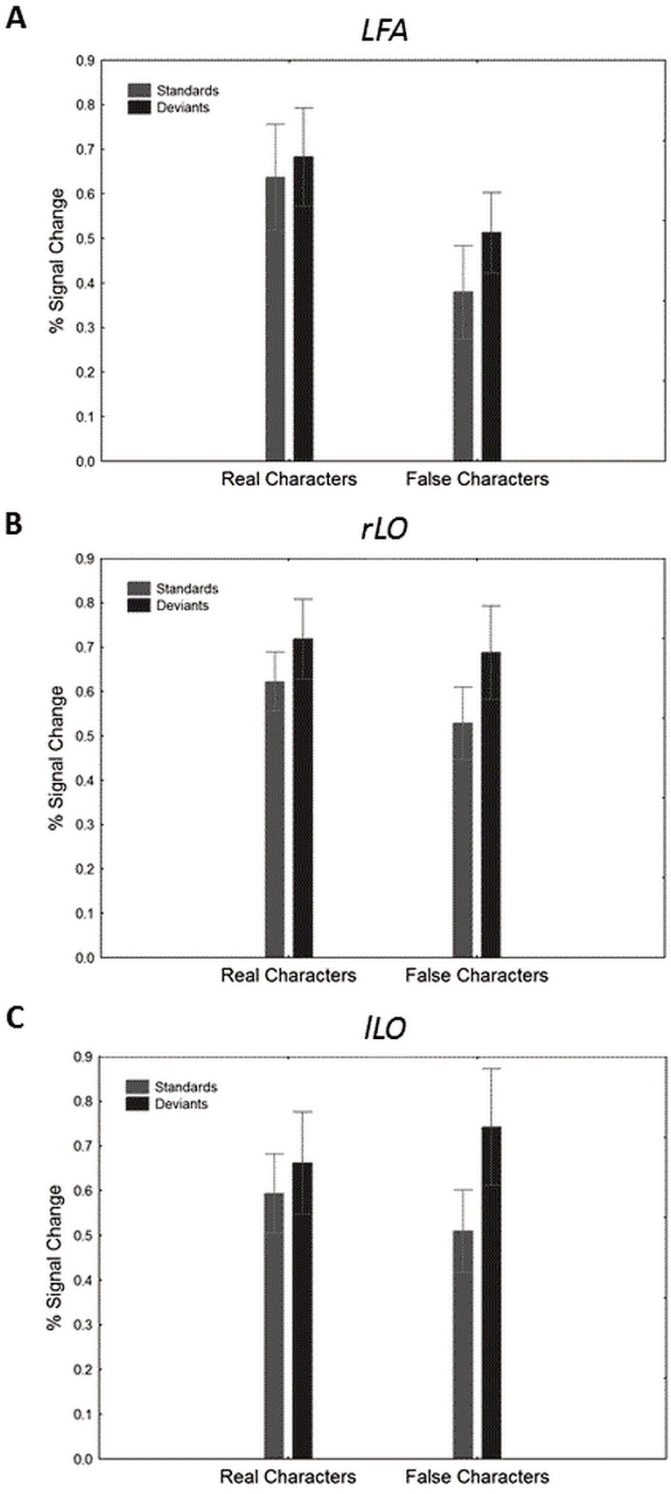

Figure E4.4 – fMRIa for real and false characters in LFA and LO: Differences between blocks with and without Deviant stimuli for real characters (left) and false characters (right) for LFA (up), right LO (middle) and left LO (down).

3.2.4 Whole-brain analysis

To test whether the difference of Standards and Deviants is encoded by other neurons outside the LFA and LO, we also performed a second-level whole-brain analysis testing for vMMN effects separately for real and false characters using a fixed threshold of $p<0.05_{FWE}$ with a cluster size >20 voxels, but no significant results were found.

To confirm that no region remained unnoticed by the commonly applied, rigorous FWE corrected threshold we also analyzed our data at a less conservative threshold ($p<0.0001_{uncorreted}$; cluster extent of >20 voxels). The whole-brain analysis with this threshold, however, did not reveal any active clusters either.

3.3 Correlations

3.3.1 Correlation analysis of the vMMN in ERP and fMRIa in neuroimaging data

The correlation analysis between the vMMN of ERP and the fMRIa of the neuroimaging data sets found significant results for the real characters. The vMMN of the CP1 cluster between 400-500ms (see Fig 3A, black box) showed a significant correlation with the fMRIa of the LFA (r=0.67, p=0.007; Fig.E4.5A). In addition, a strong trend for correlation was found with the rLO as well (r=0.46, p=0.06). These correlations suggest that the EEG and fMRI reflect similar neural processes and that the basis of the observed vMMN within this later time-window can be the signal-reduction, found in the occipito-temporal areas which are sensitive to the category of the probe stimuli. While our vMMN results also revealed a significant cluster over the occipito-temporal electrodes in an earlier time-window, at around 200-300 ms, this showed no correlation with either the fMRIa of the LFA or the rLO.

Interestingly, partial correlations indicate a strong correlation between the fMRIa of the LFA and the amplitude of the vMMN of the CP1 cluster (r=0.67, p=0.007), whereas the correlation of the vMMN amplitude at the CP1 cluster with the fMRIa of the rLO is no longer significant. No other significant results were found.

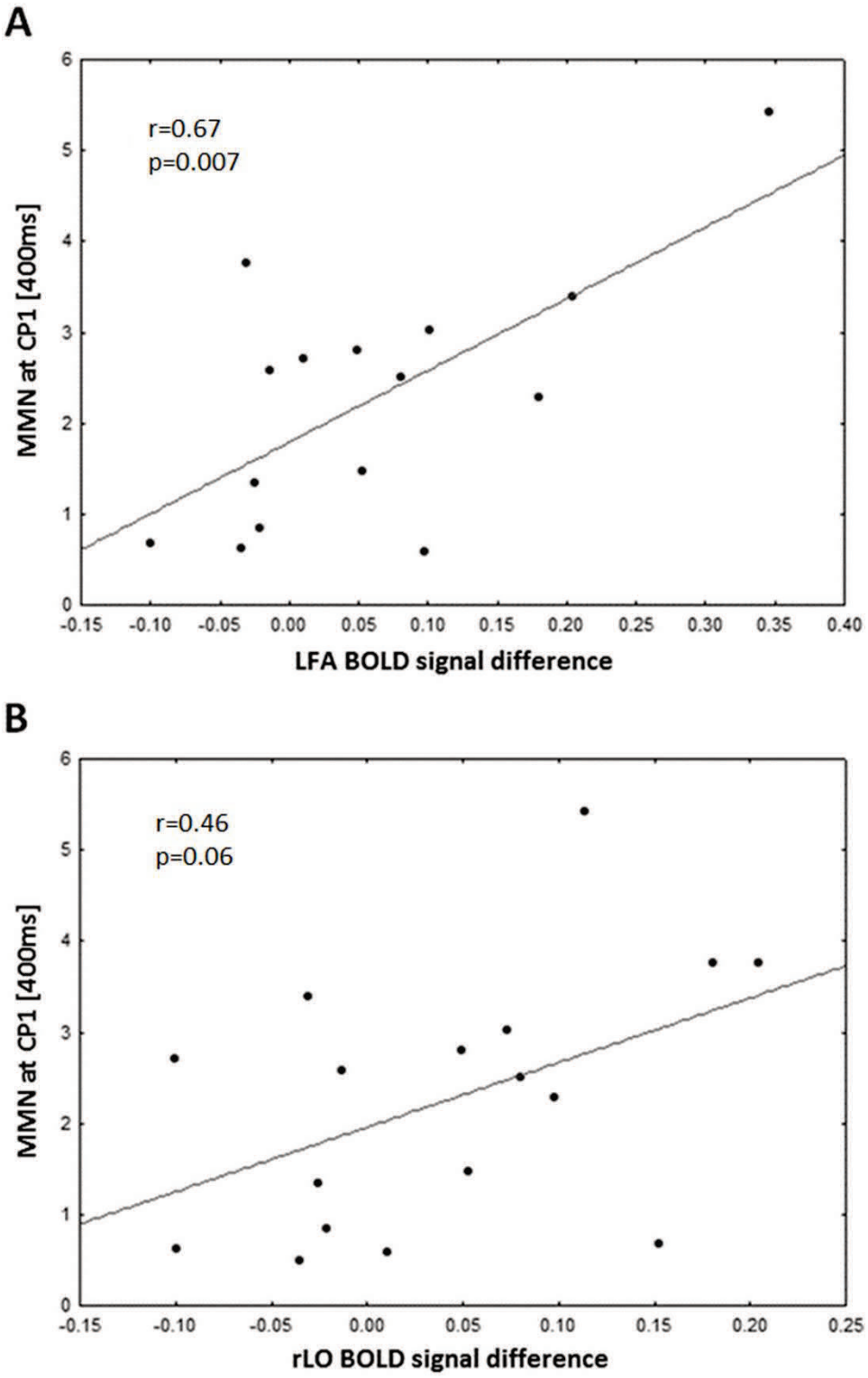

Figure E4.5 – Correlation between the vMMN for the real characters within the CP1 cluster and the fMRIa found for real characters in LFA (A) and right LO (B): x axis corresponds to the BOLD signal difference between blocks with and without Deviant stimuli for real characters for LFA (A) and right LO (B) and y axis corresponds to the vMMN (Dev-Stand) at the CP1 clusters within the 400-500ms time window.

4. Discussion

In summary, we found significant vMMN in ERPs as well as a significant fMRIa within the LFA and LO for both real and false characters. Importantly, the later part of the electrophysiologically measured vMMN and the fMRIa in the LFA showed a significant correlation for real characters, suggesting the existence of a congruent neuronal mechanism behind vMMN and fMRIa measured within the same oddball paradigm.

These findings are in accordance with theories of PC, as they were recently proposed to explain both phenomena similarly (fMRIa – Auksztulewicz & Friston, 2016 ; MMN – Auksztulewicz & Friston, 2015; Stefanics et al., 2014). Therefore, the observed correlations are in line with PC theories, explaining stimulus repetition related neural phenomena, recorded with electrophysiological and neuroimaging techniques.

However, other explanations can be used to interpret the existence of these correlations. First, it is possible that the BOLD signal merely reflects the processing of additional stimuli (two stimuli in the Deviant sequence vs one stimulus in the Standard sequence). Moreover, there is also the possibility that the correlation between the EEG and fMRI measures is mediated, indirectly, by the attentional state of the participants while performing the task. However, the two abovementioned alternative interpretations seem implausible for the following reasons: 1. If the BOLD results reflected merely the processing of an additional stimulus, then there should have been a correlation between the mismatch and adaptation for the false characters as well; 2. There were no behavioral differences between the real and false characters, at least signaled by the RT and accuracy measures. If the correlation was mediated by the participants' attentional state one would have expected either behavioral differences

or the existence of a correlation between the EEG and fMRI data sets for the false characters as well. Therefore, we believe that the PC theories are the most likely explanation for our results. Moreover, our results fit well with the assumption that expertise determines predictive stimulus encoding as only the real characters, which showed predictive modulations of the repetition suppression in a prior study (Grotheer & Kovács, 2014a; please see a detailed discussion on expertise/familiarity below), showed a significant correlation between the two data sets in our current study.

Importantly, most of the electrophysiological studies show vMMN effects in earlier time-windows (around 200ms peak; see Korpilahti et al., 2001; Morlet & Fischer, 2014). However, the current results reveal early and late vMMN effects. These differences can be explained by our hypothesis-free manner of estimating the occurrence of vMMN, which is not at all customary in the literature today (e.g. Morlet & Fischer, 2014; Schirmer & Escoffier, 2010). Our current results replicate our prior ones (Amado and Kovacs 2016) in the sense that the conventional vMMN (deviant – standard) leads to the largest differences around 400-600ms post-stimulus onset for real and false characters over the same cluster of posterior electrodes.

Interestingly, only the late vMMN showed a correlation with the data acquired with the fMRI. This time-window can be interpreted as a *late mismatch negativity* or a *late discriminative negativity* (LDN; Näätänen et al. , 1982; Cheour et al., 2001). The late MMN is also elicited by deviant stimuli in oddball paradigms and usually occurs between 400-700ms post-stimulus onset. The functional significance of this late MMN component is not clear and several explanations have been given to this effect: For example: 1. Higher cognitive processes, such as attention, letter-speech sound integration, and long-term memory (Neuhoff et al., 2012); 2. Automatic preparation

to detect additional stimuli (Näätänen et al., 1982; Mueller et al., 2008); 3. Attentional reorienting back to the original task (Schröger & Wolff, 1998; Escera et al., 2000; Munka & Berti, 2006).

Moreover, the existence of this late vMMN can also be interpreted as related to the N400. However, MMN does not depend on attention (Cammann, 1990; Stefanics et al., 2014), while N400 does (McCarthy & Nobre, 1993). Nevertheless, some findings suggest that MMN and N400 effects have certain connections. For example, there seems to be an interaction between the N400 and the frequency of word usage, i.e. less frequent words are associated with larger N400s than more frequent words (Petten & Kutas, 1990). Additionally, N400 is also larger to unexpected items in a given context (Kutas & Hillyard, 1984). Although, this effect is known to be stronger for pseudo, false than for real characters (see Lv & Wang, 2012). Therefore, this finding does not fit with the fact that we only found an ERP-fMRI correlation for the real characters. Moreover, grammatical violations (an example of environmental violations) do not elicit a large N400, instead these induce a large P600, i.e. a positivity from about 500-1000ms post stimulus onset, which we did not observe in our current design.

Furthermore, the current study is the first to report the existence of fMRIa in an oddball paradigm within cortical areas that are selective to the probe stimulus category, in this case characters of the familiar alphabet. To the best of our knowledge, there is only one (v)MMN study which integrates the electrophysiological data with fMRI recordings, using an ROI analysis approach (Hedge et al., 2015). In this visual study two areas (the inferior temporal gyrus and the middle frontal gyrus) were selected bilaterally, however the area selection was based on findings of previous auditory MMN studies and on a cortical structural atlas, instead of independent functional localizer scans. Please note that this study focus visual domain, although

the selection of the cortical areas was based on prior auditory studies. Moreover, the selected ROIs are rather large (although the ROI sizes are not specified in the article and are not personalized for each participant), as they included entire anatomical regions (i.e. either the entire inferior temporal or middle frontal gyrus). These facts make the interpretation of the results difficult.

Interestingly, only the real characters showed a significant correlation between fMRIa and vMMN in the current study. This result might be due to the commonly known association between the left hemisphere and language processes (Petersen, Fox, Posner, Mintun, & Raichle, 1988), such as the perception of characters or words (Hillis et al., 2005). In fact, the current data shows a main effect of character type in the LFA. This is in accordance with the above referred studies by showing an increased response for real characters in comparison to the false characters. Also, differences between the processing of real and false characters were detected in other neuronal phenomena (Grotheer & Kovács, 2014b), more specifically during the repetition probability modulation of RS, also known as Prep effect (Kovács et al., 2013). Briefly, this study shows Prep modulation on RS for real, but not for false characters. Previous studies reported the existence of a Prep modulation on the RS for faces (Grotheer et al., 2014; Kovács et al., 2012; Kovács et al., 2013; Larsson & Smith, 2012; Summerfield et al., 2008), but not for chairs or everyday-objects (Kovács et al., 2013). Altogether, these findings suggested that the influence of contextual predictive information might be affected by the prior experience of the participants with the stimuli. Here we show that for familiar stimuli (i.e. for stimuli with which participants had extensive prior experiences) vMMN and fMRIa correlate with each other, suggesting shared neural mechanisms while no such relationship exists for unfamiliar stimuli. Therefore, our results indirectly support further hypothesis that expertise changes the neural

mechanisms of stimulus processing, for example by facilitating the neurons to process prediction error-related signals (Grotheer & Kovács, 2014).

Besides familiarity and expertise, real and false characters also differ in meaning and multisensory associations. The false characters are novel, non-existent characters and thus not meaningful; whereas real characters have a specific associated label and they are meaningful. It is known that meaning can modulate the neural responses (Glezer et al., 2015; Pulvermüller, 2013), consequently it can also affect the obtained results. The multisensory-level differences are related to the fact that real characters can be verbalized, because there is a particular sound associated to each character. Moreover, it has been proven that the activity of language areas is organized by sound even in the absence of auditory stimuli (Magrassi et al., 2015). Hence, the meaningful and multisensory-associated characteristics of the real characters might also explain why the correlations between vMMN and fMRIa were only found for this stimulus category.

Interestingly, our results reveal differences in the ERPs of the Control condition between the real and false characters. These dissimilarities can also be explained by the above described familiarity/expertise effects. Furthermore, it is not unusual in vMMN studies to have asymmetric data for different stimulus categories or even different stimuli (Sulykos et al., 2015).

Regarding the whole brain analysis, most of the previous studies reported significant results with typical activations in the frontal cortex, more specifically (in the middle frontal, the right precentral gyri and in the medial frontal region; see Deouell, 2007). Besides, together with these frontal regions, other studies revealed significant activity in the superior temporal gyrus as well (Gomot et al., 2006; Hedge

et al., 2015; Liebenthal et al., 2003; Tse & Penney, 2008). Nonetheless, the current study revealed no significant frontal activations. The discrepancy of the current and the above referred previous studies can be due to the different: (1) domains of study which was auditory for almost all prior studies (Gomot et al., 2006; Liebenthal et al., 2003; Tse & Penney, 2008), while we focused on the visual domain or (2) stimulus categories: when compared to Hedge et al., (2015) stimuli (single and double bars) the current stimuli have higher levels of complexity, as they were characters.

In conclusion, this study shows for the first time that the magnitude of vMMN and fMRIa in the occipito-temporal cortex correlate with each other for stimuli of high familiarity. This suggests that the two phenomena have similar neural mechanisms, presumably explained by predictive coding theories.

Supplementary Material

In this section, we present the results regarding the electrophysiological results of the equiprobable, control condition. Please note, that due to the applied block design we omitted the same analysis of the BOD signal. The control condition can be used to calculate the magnitude of surprise and adaptation related response changes separately (Kaliukhovich & Vogels, 2014).

Here we only measure the surprise related MMN components as it has been shown to underlie conventional vMMN for character stimuli (Amado & Kovács, 2016b). To determine the surprise related vMMN, the difference between Deviant and Control conditions of the same stimuli (i.e. real or false characters as both Deviants and Controls) was calculated (Dev-Control). A similar procedure was employed to determine the repetition related response of the vMMN, by calculating the difference between the Control and the Standard, i.e. Control-Standard.

Furthermore, in order to estimate the amount of the vMMN that overlaps with surprise enhancement and thus, can be explained by an underlying surprise mechanism (Amado & Kovács, 2016) we calculated the percentage of the significant difference in the statistical plots of the vMMN for the Dev-Control condition for both real and false characters separately. To this end, we considered the significant differences of the vMMN statistical plots as 100% and calculated the percentage of significant vMMN time points which were overlapping with the Dev-Control (surprise or "genuine" vMMN) statistical plots (for further details see Amado & Kovács, 2016b). Additionally, to quantify the dependence of the vMMN on surprise related mechanisms, we correlated the ERP wave differences of the two effects (vMMN: Dev-Stand and surprise: Dev-Control) with each other and for each category separately.

Note that the correlations of the vMMN with the Dev-Control differences were only performed for the time-windows in which the vMMN could be explained by surprise (this we call as “genuine” vMMN) or in other words, when the vMMN was overlapping with the surprise effects (Dev-Control). The same approach was used to calculate the relationship of vMMN with repetition related effects from the standard (RS; Control-Stand) as well.

For the behavioral data, the repeated measures ANOVAs were done only with one factor (the sequence, 3) and hence compared the equiprobable condition with the oddball and reversed oddball conditions, similarly as Amado & Kovács, (2016).

S.1. ERP

S.1.1. Behavior

The performance was significantly reduced for the equiprobable sequences when compared to the other sequences ($F_{2,32}$=11.5, P<0.001, ηp^2=0.42): , i.e. oddball (Fisher LSD *post hoc* test: P<0.01) and reversed oddball (Fisher LSD *post hoc* test: P<1e-3) of the real and false characters stimulus pair. Furthermore, the reaction times showed a main effect of sequence ($F_{2,32}$=32.3, P<1e-7, ηp^2=0.67) complementary to the main effect found for the performance. In other words, reaction times of the equiprobable sequences were significantly longer when compared to the oddball (Fisher LSD *post hoc* test: P<1e-7) and reversed oddball conditions (Fisher LSD *post hoc* test: P<1e-7). These differences might be due to the existence of more stimuli in the equiprobable sequence resulting in an irregular background which might increase the difficulty of the given task.

S.1.2. Surprise enhancement (Deviant-Control)

We found significant Deviant-Control differences within the 187-755ms and 73-702ms time-windows for real and false characters, respectively (Fig.E4.6). Interestingly and as for the conventional vMMN effects, the time by electrode statistical plots are extremely similar for the two character groups. More importantly, most of the significant electrodes and time-ranges of these surprise enhancement effects (Fig.E4.6) are similar to the vMMN effects (Fig.E4.3) for both real and false characters. These results confirm our previous findings with character stimuli (Amado & Kovács, 2016).

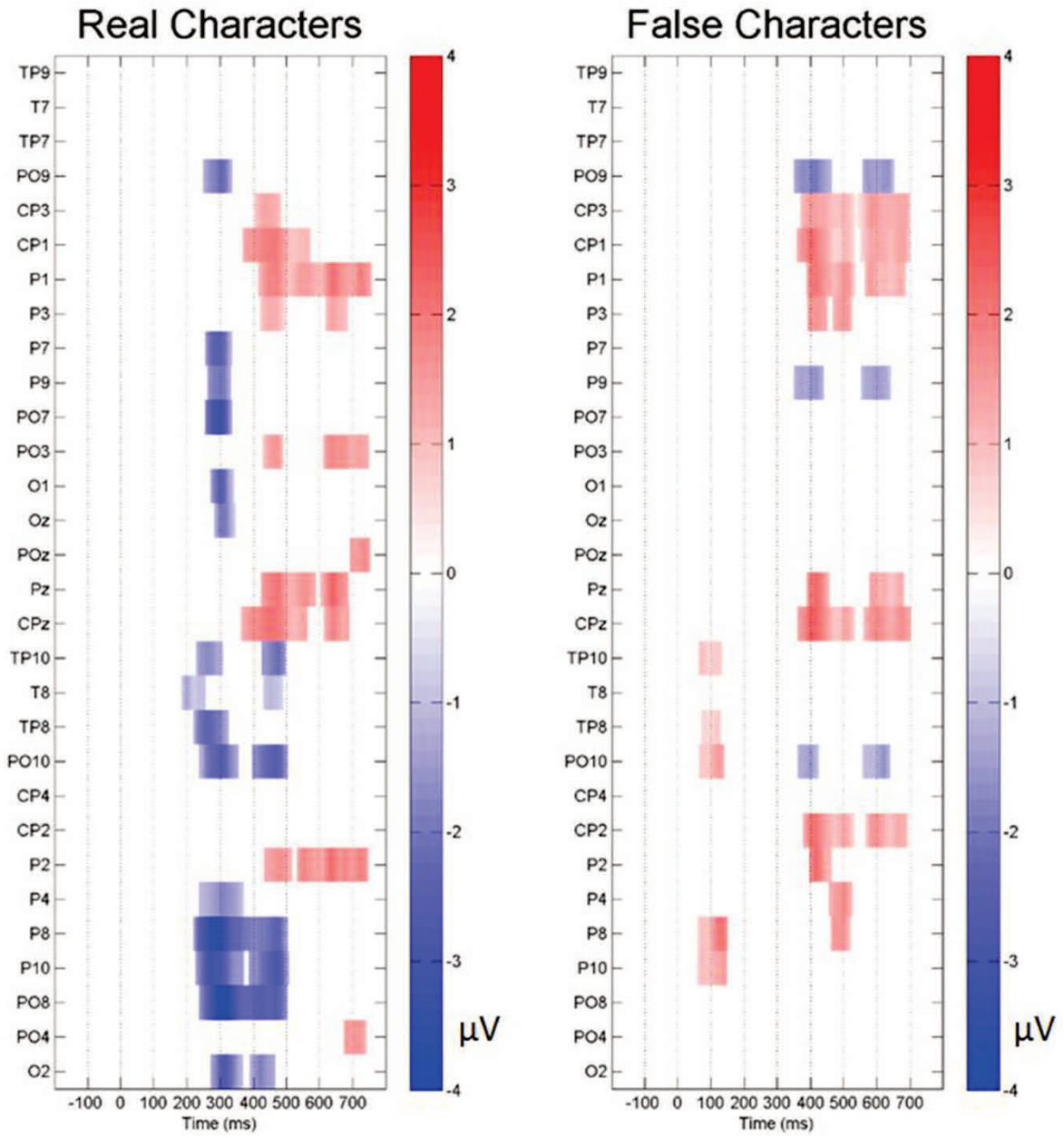

Figure E4.6 – Surprise Effect - Differences between deviant and control stimuli for real characters (left) and false characters (right) plotted in time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference).

S.1.3. Repetition Suppression (Control-Standard)

We found significant Control-Standard differences within the 24-613 ms and 158-744 ms time-windows for real and false characters, respectively (Fig.E4.7). Interestingly, the time by electrode statistical plots are dissimilar for the two character groups. More importantly, most of the significant electrodes and time-ranges of these repetition related effects (Fig.E4.7) do not match the vMMN effects (Fig.E4.3).

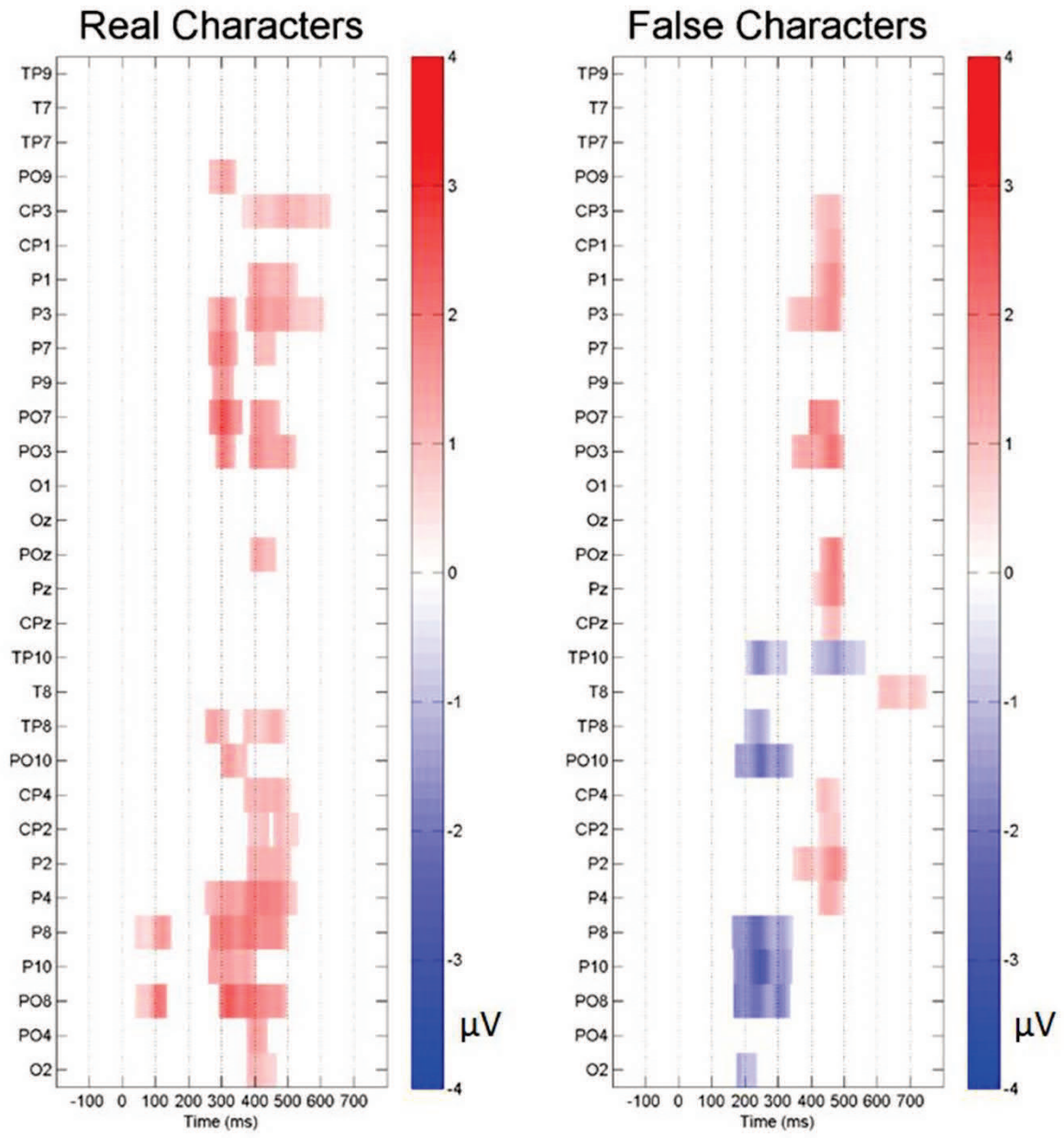

Figure E4.7 – Repetition suppression effect - Differences between control and standard stimuli for real characters (left) and false characters (right) plotted in time by electrode statistical plots (color-coded as a function of the amplitude of ERP difference).

S.1.4. Correlation of the conventional vMMN with surprise and with RS

The comparison of the vMMN to the RS and surprise related differences revealed that more than 40% of the conventional vMMN effects are explained by surprise for real characters and the correlation of these two effects is robust and significant (Table E4.1). On other hand, the vMMN that was observed for false character stimuli overlapped equally with RS and surprise. In addition, the vMMN of real characters also overlapped with some RS related effects, however, the correlation of the vMMN with RS was not significant. Interestingly, false characters showed high correlation between RS and surprise effects as well. These results replicate and confirm the previous findings of Amado & Kovács, (2016).

Table E4.1 – Percentages and Correlations of vMMN with RS and Surprise

	Comparison	Real Characters	False Characters
All Standards	MMN & RS	17.5% (R=0.9; p=8E-15)	28.9% (R=0.74; p=5E-4)
	MMN & Surprise	41.21% (R=0.86; p=3E-5)	23.1% (R=0.81; p=0.04)

S.2. fMRI

S.2.1. Whole-brain analysis

To test which areas encoded the difference of the Control stimuli against Standards and Deviants, we performed a second-level whole-brain analysis testing these differences, separately, for real and false characters using a fixed threshold of $p<0.05_{FWE}$ with a cluster size >20 voxels, but no significant results were found.

To confirm that no region remained unnoticed by the commonly applied, rigorous FWE corrected threshold we also analysed our data at a less conservative threshold ($p<0.0001_{uncorreted}$; cluster extent of >20 voxels). The whole-brain analysis with this threshold revealed significant differences (please see the Table E4.2 and Fig. E4.8). Both, real and false characters show larger BOLD responses for the Control condition than the Standard condition in certain cerebellar areas (Fig.E4.8A and Fig.E4.8B). When comparing the Control and Deviant conditions, the real character stimuli showed no significant differences, however the false characters led to a similar pattern of activation within the cerebellum.

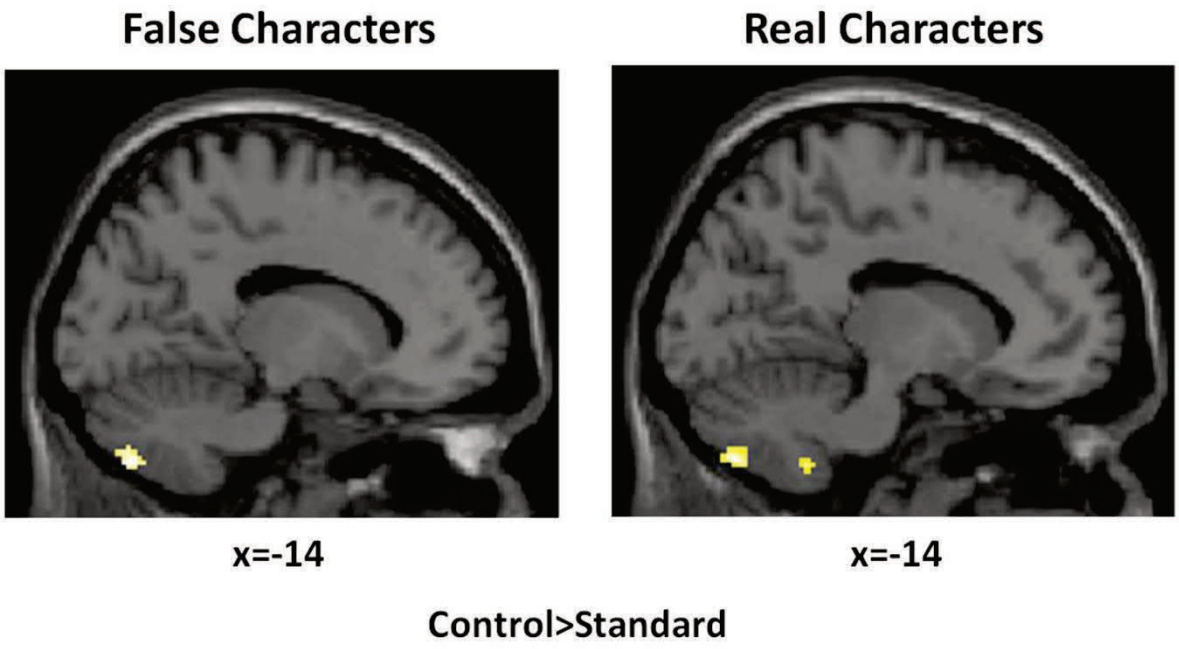

Figure E4.8 – Activations in the whole-brain analysis. Statistical parametrical maps of the contrast Control>Standard for false (left) and real characters (right).

Table E4 2. Summary of significant activations in the whole-brain analysis

Category	Contrast	Brain Region	Coordinates	Cluster size	Threshold
False Characters	*Control* >Standard	Inferior Semilunar Lobule	-14, -74, -46	75	(p<0.0001 unc)
False Characters	*Control* >Deviant	Inferior Semilunar Lobule	-14, -74, -46	20	(p<0.0001 unc)
Real Characters	*Control* >Standard	Inferior Semilunar Lobule	-12, -76, -46	61	(p<0.0001 unc)
Real Characters	*Control* >Standard	Cerebellar Tonsil	18, -46, -46	76	(p<0.0001 unc)
Real Characters	*Control* >Standard	Ulva	10, -7, -42	66	(p<0.0001 unc)
Real Characters	*Control* >Standard	Cerebellar Tonsil	18, -46, -46	27	(p<0.0001 unc)

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III General Discussion

The aim of the current work was to examine the mechanisms and connections of two phenomena (RS and MMN) in the ventral visual pathway in humans. Four studies were used to address this issue. The first two studies dealt with the RS phenomenon, while the other two addressed the nature of the MMN measured in a typical oddball paradigm.

It was not clear what temporal dynamics underlie the prediction and RS effects. In order to address this question, in the second study (Section II 2), we presented our subjects with expected and surprising stimulus pairs with two different ISIs (0.5s for Immediate and 1.75 or 3.75s for Delayed target presentation). We found that the prediction effects do not depend on the length of the ISI period. These results suggest that Immediate and Delayed cue-target stimulus arrangements create similar expectation effects in the face sensitive visual cortex.

In our second study (section II 2), we hypothesized that predictions can induce the neuronal differences between correctly and incorrectly predicted events either by surprise enhancement or via expectation suppression. Hence, we presented repeating or alternating pairs of faces and divided them into three conditions: correctly predicted (expected condition), neutral (unpredicted) and incorrectly predicted (surprise condition). Please note that the unpredicted, neutral trials were used as a control condition, to which the correctly and incorrectly predicted trials were compared. We found larger BOLD responses to the incorrectly predicted, surprising trials than to the unpredicted, neutral ones. Our results suggest that predictions affect the neuronal responses via surprise enhancement instead of expectation suppression.

Also, in typical oddball paradigms, the vMMN phenomenon depends on the repetition probability. In the third (Experiment 3), we hypothesized that MMN can be modulated by expertise and/or it can be category dependent. To clarify this question,

we employed a conventional oddball paradigm arranged into two stimulus pairs (1. Faces vs Chairs and 2. Real vs False Characters). However, the main aim of this third experiment was similar to that of the Experiment 1, i.e. to disentangle which neural mechanism underlies vMMN: a surprise related response enhancement or a repetition related suppression. To answer this question, we compared the responses to the stimuli presented in conventional oddball sequences to the same stimuli in equiprobable, control sequences (Kaliukhovich and Vogels, 2014). We hypothesised that the vMMN would be due to repetition-related effects if the standards responses are reduced when compared to those in the equiprobable condition, whereas vMMN would be explained by a surprise enhancement if the deviant responses are larger than those in the control condition. We found that the neural mechanisms underlying MMN are category dependent; however these mechanisms do not co-vary according the stimulus expertise. Briefly, the vMMN of faces and chairs was driven by RS; whereas vMMN of real and false characters was mainly due to surprise-related changes.

Finally, both fMRIa and MMN are related to predictions about the environment. However, so far, no study used category-specific ROIs to investigate the link between the vMMN and fMRIa within the same paradigm and participants. To address this matter, in our fourth study (section II 4), we recorded fMRI and EEG data for characters from the same participant with an oddball paradigm. We found a significant correlation between MMN (CP1 cluster at 400 ms) and fMRIa (letter form area, real characters), which constitutes evidence for their robust relationship.

As most of our results suggest the dominant role of surprise in determining prediction related phenomena, I will deeply discuss how surprise modulates both RS and (v)MMN (Section III 1). Finally, I will point out the experimental limitations (Section III 2) as well as future perspectives and open questions (Section III 3).

1 The role of surprise in predictive-related phenomena

The most important finding of the current thesis is the fact that prediction related phenomena are mostly originated from surprise enhancement rather than by expectation suppression. Three of the studies in this thesis used neutral, non-predicted control conditions to infer such conclusions and to show how surprise modulates predictions. In this section, the role of surprise as a top-down mechanism is discussed, along with the two prediction related phenomena: RS (III 1.1.) and MMN (III 1.2.). Finally, I will propose a unification of these phenomena within a predicrtive coding framework (III 1.3.).

1.1 Repetition suppression and surprise

In terms of cue-based expectations our results show that an enhancement of the BOLD responses occurs for surprising, incorrectly predicted events in comparison to the neutral and correctly predicted conditions for alternation trials only (Experiment 2). These results are in line with what has been found by Egner and colleagues (2010), who reported that surprise enhancement has a larger contribution on the prediction effects of face stimulus than expectation suppression. However, their pioneer study only focused on perceptual predictions, while our experiment investigated RS phenomena in addition to expectation effects, and how they are modulated by perceptual expectations. Interestingly, the experimental results show that surprise enhancement only modulated alternation trials. The natural follow-up question is then "why do perceptual expectations affect alternation trials rather than repeating ones?". Unfortunately, Experiment 2 can only clarify the mechanism behind perceptual expectations of the alternation trials (i.e. surprise enhancement). It is important to emphazise that our results match what can be found in most of the studies investigating effects of Prep modulation on RS, i.e. larger BOLD signal for alternation trials in repeated blocks when compared with alternation trials in alternating blocks (see Grotheer and Kovács, 2014; Grotheer et al., 2014; Kovács et al., 2012, 2013; Larsson and Smith, 2012; Summerfield et al., 2008). These studies are not so consistent in terms of the effects of implicit expectations on repeated trials (Rep), either. For example, some experiments revealed no interaction of implicit predictions on Rep as the BOLD response for these trials was similar in repeated and alternating blocks (Grotheer and Kovács, 2014- LFA; Grotheer et al., 2014; Kovács et al., 2013– OFA and LO; Kovács et al., 2012 – overlapping condition). However, other studies show Prep modulation on RS thought to be due to two effects: 1. surprise enhancement of the alternating trials (in the repetition blocks); 2. expectation suppression of the repeated

trials when presented in repetition blocks in comparison of those when presented in alternating ones, due to observed smaller BOLD responses (Kovács et al., 2012; Larsson and Smith, 2012; Summerfield et al., 2008 – non-overlapping condition; Kovács et al., 2013 - FFA). Furthermore, in one of the cited studies (Grotheer and Kovács, 2014) the Prep modulation on RS in LO is due to a smaller BOLD response for alternation trials in alternating blocks than in repetition blocks. Also, a recent study showed Prep modulation on RS, which, in fact, only depended on the repeated trials with larger BOLD signal for these when presented in alternating blocks than when delivered in repeated blocks (Pajani et al., 2017).

It is of note that other studies revealed no interaction between cue-based, explicit expectations and RS, which means that, in this case, both alternation and repetition trials were affected by predictions (Experiment 1; Grotheer and Kovács, 2015; Todorovic and Lange, 2012). Hence, further studies (with a control condition) are necessary to elucidate which mechanisms (for a schematic see Fig. D 1) induce the Prep modulation for both repetition and alternating trials in terms of implicit expectations. Overall, the finding that surprise enhancement induces the explicit prediction effects on alternating trials fits with the existing literature on implicit expectations. Yet, other experiments could confirm the similarity in terms of mechanisms for these two types of expectations within ROIs, stimulus category and task, for example.

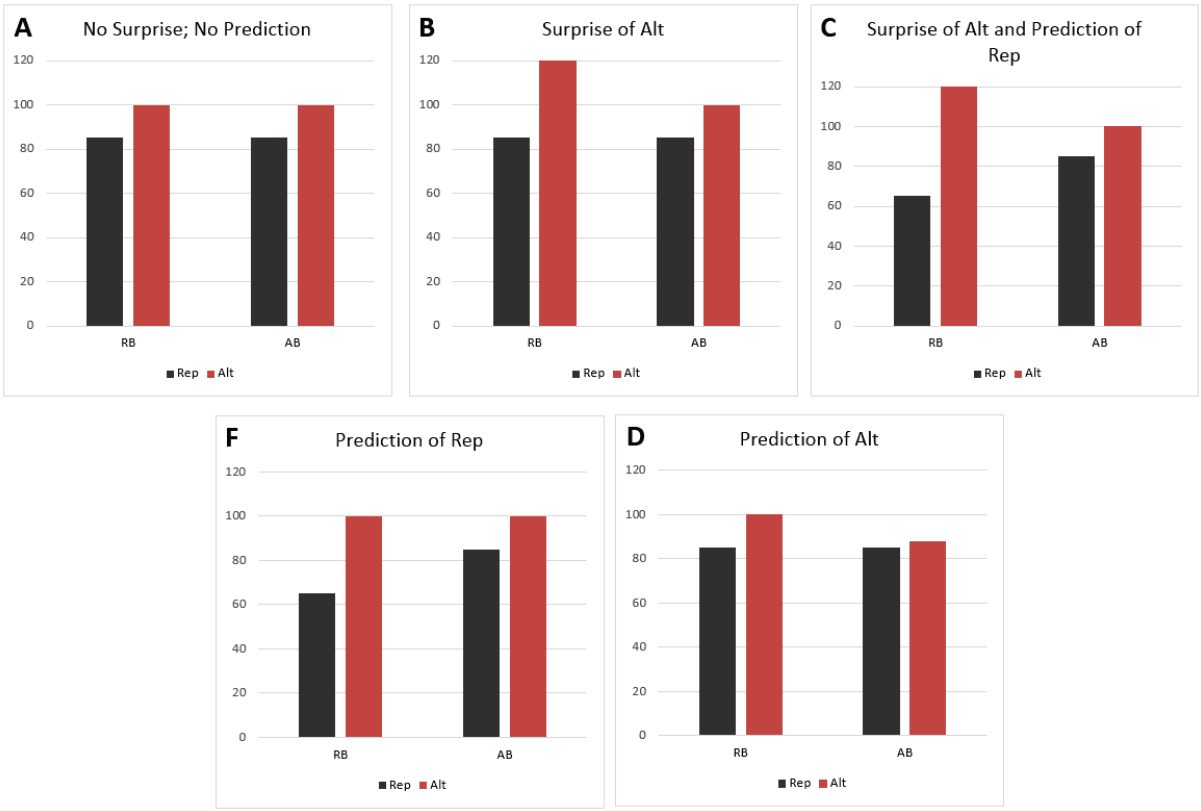

Figure D 1 - Schematic illustrations of how implicit top-down modulations (predictions and surprise-related) might affect neural responses. Hypothetical BOLD signal is presented separately for the repetition (black, Rep) and alternating (red, Alt) trials in blocks with high probability of repetitions (repetition blocks, RB) and low probability of repetition (alternation blocks, AB). **A.** Repetition suppression is independent of predictions or surprise (of Alt or Rep). Repetition suppression index (RSI) is larger for RB than AB, due to: **B.** surprise enhancement response to Alt in RB (surprise of Alt); **C.** expectation suppression of Rep in RB (prediction of Rep) and surprise enhancement response to Alt in RB; **D.** expectation suppression of Alt in AB (prediction of Alt); **E.** expectation suppression of Rep in RB.

1.2 Mismatch negativity and surprise

The third and the fourth experiments of the current thesis show that surprise enhancement drives vMMN for real and false characters. Indeed, other experiments also reveal "genuine" (v)MMN, i.e. the existence of genuine surprise related responses to deviants in oddball sequences (see Winkler, 2007; Stefanics et al., 2014). Additionally, these findings support prior experiments that show a MMN response for deviants that are in fact an omission of the stimulus (Nordby, 1991; Yabe et al., 1997, 1998; Wacongne et al., 2012). Still, when the oddball paradigm used to induce (v)MMN employs the omission of a stimulus as a deviant, the violation of regularities can be due to two predictions: the prediction of a tone and the higher expectation of its deviancy. This is due to the experimental design that included a block with a sequence of five tones is presented (in 75% of trials), interspersed with rare violations (in 15%) in which the frequency of the fifth tone deviates from the expected, and with rare omissions (in 10%) in which the fifth tone is simply omitted. Hence, the common MMN design to investigate omission cannot separate the surprise related response to omission of the two prediction types (i.e. the existence of a tone and its deviancy). A recent experiment also studied predictive processes by omitting the expected sensory input (SanMiguel et al., 2013), where a button press provided information on the nature of the upcoming stimulus and on its precise time of occurrence, allowing for neuronal responses of these two predictions types to be disentangled. Here, no oddball paradigm was used, but 3 types of events could happen: exogenous response (stimulus not caused by own action); fulfilled prediction (stimulus caused by own action) and prediction error (omission of stimulus caused by own action). Briefly, the exogenous response represents the low level information that is feedforwarded to high level regions without time-locked predictions. The other two conditions, on another hand, have time-locked

predictions, since the stimulus is generated by the participants' action, which either can be fulfilled (activating the prediction via top-down signals) or not fulfilled (inducing a prediction error through bottom-up transmissions). This study has revealed the neural representation of prediction by omitting the predicted sensory input. Electrophysiological data shows that a formulation of a clear prediction elicits the activation of its template response to the predicted stimulus (before the actual stimulation). A surprise response was found for both prediction types.

In contrast, the results of our third experiment suggest the dominant role of adaptation in underlying the vMMN phenomena for faces and chairs. Other studies reveal no genuine MMN, i.e. no surprise response to the deviants in oddball sequences (Farley et al., 2010; Fishman and Steinschneider, 2012; May and Tiitinen, 2001; May et al., 1999; for a review see May and Tiitinen, 2010; Kaliukhovich and Vogels, 2014). This wealth of conflicting empirical evidence is paralleled by the reported results on RS literature regarding implicit and explicit expectations.

Overall, it is clear that surprise is important to prediction related phenomena; however, further studies are necessary to clarify its fundamental role.

1.3 Unification of repetition suppression and mismatch negativity within a predictive coding framework

According to efficient coding (Atick, 1992), predictive theories, which rely on Bayesian probability theory, might provide a reunion between the two neuronal phenomena investigated in this thesis, i.e. RS and MMN. Taking all four studies of the current dissertation into account (Experiment 1,2, 3 and 4), I suggest that it is possible to unify the neuronal phenomena signalling the influence of temporal context on perception (i.e. RS and MMN), in the context of predictive theories. In MMN studies predictions can be induced by the repetition of low-level (simple, physical sensory) or high-level (abstract) features (see Paavilainen, 2013 and Stefanics, 2014 for a review).

One possible interpretation of the findings of the current experiments is the following: when the predictions are based on low-level features (which are usually modulated by the manipulation of the repetition probability), basic predictive phenomena (e.g. similar to the one underlying the implicit expectations that are also induced by Prep) modulate the (v)MMN response. The predictive processes underlying higher-level, abstract MMN might be connected to those of higher-order prediction processes described in the two-stage model (Grotheer and Kovács, 2016). Indeed, the existing neuroimaging studies that investigate auditory change detection with oddball paradigms only show frontal activations for higher-order oddballs such as pitch (Molholm et al., 2005; Gomot et al., 2006; for a review see Deouell, 2007) and duration (Molholm et al., 2005; for a review see Deouell, 2007)). When the oddball paradigm relies on the low-level feature of repetition probability (i.e. passive oddball), frontal areas are not involved in change detection (Liebenthal et al., 2003). In the case of vMMN, the current neuroimaging studies exclusively employed simple oddball paradigms that are based on repetition (Experiment 4 and Hedge et al., 2015).

However, these two studies show different results regarding the role of frontal regions in vMMN, as Hedge and colleagues report frontal activations, while the Experiment 4 shows none. Such conflicting results can be due to stimulus differences, as different stimulus categories have been employed: stimuli (single and double bars) and characters. Hence, it is necessary to better understand what modulates the prefrontal activations in change dectection and whether that is consistent across sensory domains.

Still, the connection between high-level MMN and explicit expectation processes has not been tested yet. In order to clarify these, it would be necessary to study the neuronal correlates of high order MMN and those of explicit expectations with neuroimaging techniques. Also, similarly to Experiment 4, it is possible to acquire data of the same participants to study different phenomenon of interest (i.e. high order MMN as well as explicit expectations).

This way, both low and high level predictions can be defined under the predictive coding framework. Therefore, this unification needs to consider that (v)MMN also includes the two types of predictive mechanisms defined in the two-stage model (Grotheer and Kovács).

2 Limitations of the current experiments

2.1 Experimental design

2.1.1 Behavioural data

The few existing studies on the relationship between cue-based predictions and RS exclusively asserted that attention was similar between the different conditions (i.e. correctly and incorrectly predicted conditions) using catch trials (Grotheer & Kovács, 2015; Todorovic & de Lange, 2012; sections II 1 and II 2). Briefly, in these trials participants had to report a particular feature of the first stimulus of a pair (S1), for example: the gender of the face (Grotheer & Kovács, 2015; sections II 1 and II 2) or the pitch of the tone (Todorovic & de Lange, 2012). Such features were directly related to the creation of the predictions, because, for example, female faces predicted repetition and male faces predicted the alternation of S2 (Grotheer & Kovács, 2015; sections II 1 and II 2). In other words, once S1 was perceived, a prediction about S2 could be formed. Therefore, accurate perception of these features was crucial to the creation of the intended predictions.

However, it is possible that some results originate originate from a certain mismatch between the original experimental intent (e.g. the expectation of repetition/alternation by the correct identification of the S1 cueing feature – gender/pitch) and the actually created predictions (e.g. the expectation of alternation/repetition due to the incorrect identification the S1 cueing feature). Usually, in these experimental designs, incorrectly predicted events and correctly predicted events have 25% and 75% of probability, respectively. Therefore, if there are more inaccurate S1 feature perception trials for either expected/unexpected conditions, the probability ratio of these conditions would also change (following the

example the number of expected/unexpected trials would decrease and inversely increase for the other condition).

It is important to note that this issue depends, of course, on the difficulty of the given tasks, i.e. the accuracy of the stimulus feature detection. For example, Egner and colleagues (2010) studied cue-based expectations and used the different colours of frames as cues (for example green frames cued faces and blue frames cued houses). These cues are more straightforward and easier to accurately perceive when compared with gender of faces or even pitch of tones cues (Todorovic and Lange, 2012).

It is also possible that some errors in the behavioral responses are accidental mistakes of the participants, which can arise due to fatigue or inattenrion or similar. For example, it might be that the participants wanted to report that S1 was female but accidently pressed the male response button. By becoming aware of the accidentally wrong response right after replying, the intended predictions could be created even if the behavioral response is inaccurate.

Further studies could control for this effect by measuring behavioural responses for every trial and excluding trials in which there is a mismatch between the created and intended predictions. This solution would only solve the possible mismatch between the created and intended predictions, because a different probability ration between the conditions would still be an issue. To solve the probability discrepancy there would need to be an automatic experimental change, i.e. trial to trial, to correct the ration according to the previous behavioural response.

2.1.2 Implicit versus explicit expectations on RS

It is already known that implicit expectations modulate RS and that explicit expectation (i.e. cue-based predictions) and RS effects are independent. Yet, no study tested if there is an interaction between the probabilistic implicit and the cue-based explicit expectations on RS (see Grotheer and Kovács, 2016). So far, only a few behavioural studies investigated implicit and explicit expectations within the same experimental design (Buckingham and MacDonald, 2016) or study (Droit-Volet and Coull, 2016). Buckingham & MacDonald (2016) found that implicit, rather than explicit expectations produce the size-weight illusion. Droit-Volet & Coull (2016) showed distinct developmental trajectories for explicit and implicit timing in a way that the variability of implicit timing was constant across different age groups and unrelated to cognitive capacity. The variability of explicit timing, on other hand, was higher for 5-year-olds than for 8 year-olds, and such high variability was directly linked to their limited cognitive capacity. Other time-perception fMRI studies were analyzed in a review (Coull and Nobre, 2008), showing a clear dissociation of the neural substrates for implicit and explicit perceptual timing processes.

Memory studies have a long tradition of research in the field of implicit and explicit processes. Some studies show different neural correlates of the two processes (Schacter et al., 1993; Geyer et al., 2013; Reber, 2013; Rugg et al., 1998; Ward et al., 2013), although there is also proof for overlapping mechanisms of implicit and explicit memory processes (McBride et al., 2013; Starns et al., 2012). Furthermore, Pezdek and colleagues (1989) found that memory processes depend on the expectation level in a way that items/events inconsistent with expectations have a higher recognition rate than items/events which are consistent with expectations. Therefore, there might as well be a connection between the implicit and explicit processes of memory and the

expectation of future events.

2.2 Methodological limitations

Regarding the chosen methodological approach, neuroimaging and electrophysiological techniques have different limitations which might have affected the obtained result pattern.

2.2.1 fMRI

fMRI was the chosen technique for three studies because it has great advantages specially due to its non-invasiveness and its good spatial resolution. Many other studies on the relationship between predictions and RS also use fMRI (Grotheer et al., 2014; Grotheer & Kovács, 2014, 2015; Kovács et al., 2012; Kovács et al., 2013; Larsson & Smith, 2012; Summerfield et al., 2008). Still, other techiques, such as EEG (Summerfield et al., 2006b) and MEG (Todorovic et al., 2011b) have been employed to investigate the link between predictions and RS. MMN studies investigating the neural correlates of change detection almost exclusively employ fMRI. However, it is important to note that BOLD responses are an indirect measurement of neuronal activity. fMRI measures changes in the oxygenation level of haemoglobin (BOLD), which is connected with neuronal activity (for a recent review see Buxton, 2013) since the maintenance of neuronal activity requires addictional oxygen. Recent empirical evidence indicates that the BOLD signal of a given area mirrors the neuronal response of that same region (for review see Goense and Logothetis, 2008; Logothetis, 2008; Logothetis et al., 2001; Magri et al., 2012).

Another challenge of the fMRI technique is the combination of results across subjects, through a whole-brain analysis. There is high within-subject variability of brain morphology and functional organization, even in healthy participants. The

differences are so large that no two subjects have the same neural activation at the same location in response to the same stimulus (see Fig. D 2, Allen et al., 2012). Therefore, this inter-subject variability restricts inferences at the group-level, i.e. the whole-brain analysis that was performed in the studies presented on the current thesis. This constraint happens because the average activation patterns may fail to represent the individual patterns. Please note that even when there is a normalization step that equalizes the brains of the different participants into a single, standardized coordinate system (MNI or Talairach), there is still variability between subjects regarding brain morphology and functional organization. This limitation is probably influencing the whole-brain analysis performed in three different experiments of this thesis. Due to the inter-subject variability, the current results of the whole-brain analysis might have been affect in several ways: 1. a significant effect is driven by a few subjects only; 2. a statistically significant group effect is not significant in any single subject; 3. a non-significant group effect reflects heterogeneity in the population with one subgroup of subjects responding differently to other subjects (see Seghier and Price, 2016). Together, these possibilities indicate how the inter-subject variability can influence the results and lead to wrong experimental conclusions. However, our data was not affected by effects driven by a few subjects or by effects that are not significant in a single subject, because individual statistical maps are first thresholded and then summed across all subjects (Burton et al., 2008; Fedorenko et al., 2010; Havel et al., 2006; Seghier et al., 2008a, 2008b; Spiridon et al., 2006). This method makes sure that a very consistent voxel activated in almost all subjects appears with a high value in the generated overlap map. However, the overlap map can exclude an effect due to the variability in the spatial location of activated voxels across subjects, which is likely to have happened in the presented whole-brain analysis. Please note that further studies should perform an extra analysis to complement the standard whole-brain

analyses and infer the consistency of the results across subjects (Allen et al., 2012; Seghier and Price, 2016; Xu et al., 2009).

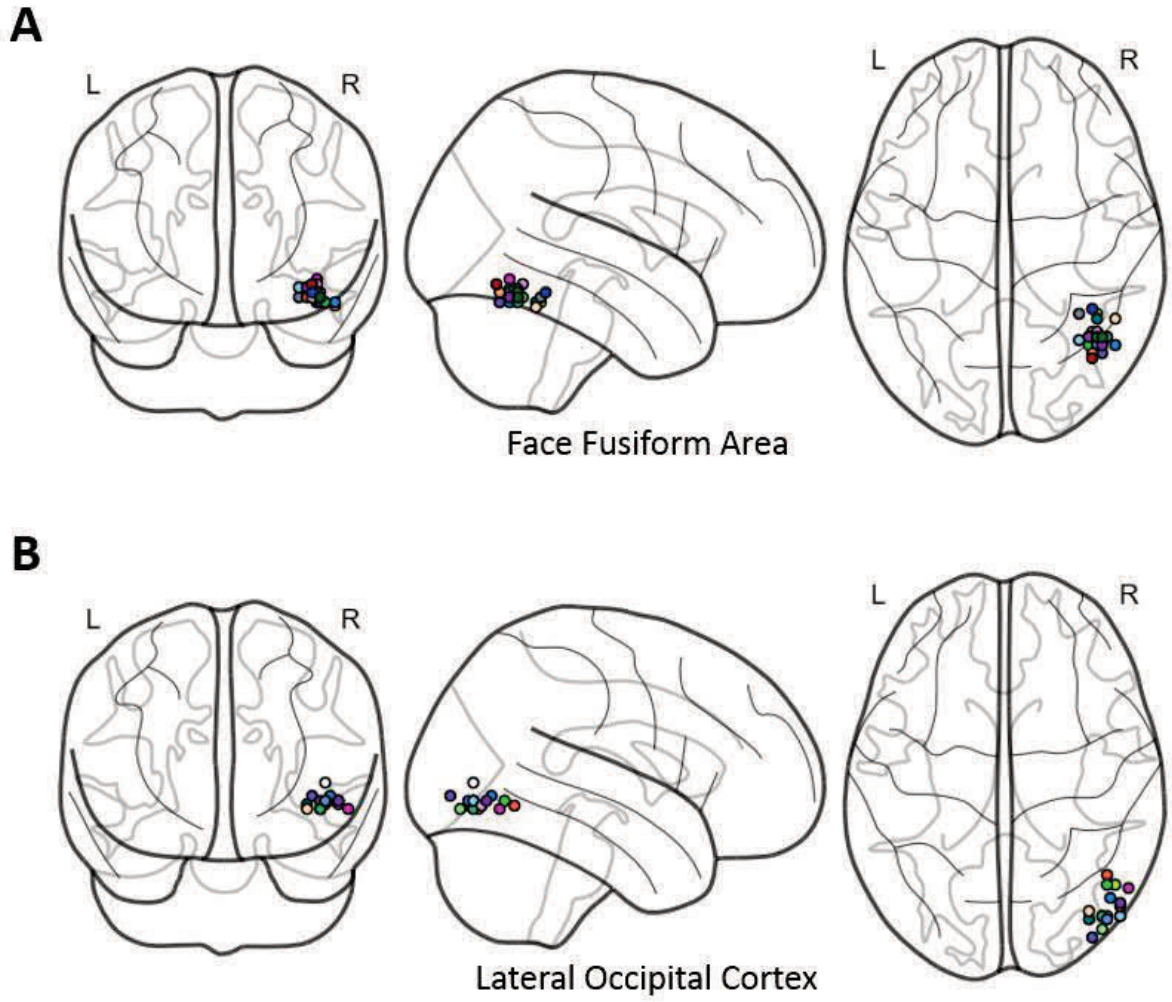

Figure D 2 – Schematic of all the fROIs used in Experiment 2 and 4. Right Face Fusiform Area (A, N=22) and right Lateral Occipital Cortex (B, N=17).

Another similarity between the presented experiments using fMRI is a region of interest (ROI) based approach, which relies on the identification of individual functional ROIs (fROIs) with a separate functional localizer run (Grotheer and Kovács, 2014, 2015; Grotheer et al., 2014; Kovács et al., 2012, 2013; Larsson and Smith, 2012;

Summerfield et al., 2008). This methodological approach enables the examination of specific and clear hypotheses, given the inter-subject variability the statistical power achieved with fROIs is much larger than the one attained with standard whole-brain analyses (Berman et al., 2010; Saxe et al., 2006). Hence, the functional properties of fROIs are suggested to be consistent between subjects. Furthermore, the usage of individual fROIs has been suggested to generate conclusions more "close to reality" and is considered "good practice" when compared with anatomically defined ROIs (Nieto-Castañón and Fedorenko, 2012; Saxe et al., 2006). However, the advantages of the fROIs are also under debate (Friston et al., 2006; Saxe et al., 2006; Weiner and Grill-Spector, 2012). Briefly, the arguments against individual fROIs are: lack of anatomical specificity; constrains on functional anatomy due to task dependence. It is undeniable that the usage of fROIs is based on the notion that there is consistency in the site of fROIs across sessions and tasks for all subjects. Indeed, within-subject variability of object and word selective regions depends on the exactness of the applied statistics (Duncan et al., 2009). Stability in the location of the FFA fROIs within-subjects was also found across experimental tasks (Berman et al., 2010). Interestingly, these studies suggested that the threshold and the stimuli used as contrast has impact on the extent and reliability of the fROIs localization. Further, it has been proposed that the inter-subject variability of the anatomical location of the fROI is due to artifacts and spatial smoothing (Weiner and Grill-Spector, 2012). However, recent research showed a close relationship between fROIs in the ventral temporal cortex and its anatomical structures (for a review see Grill-Spector and Weiner, 2014).

2.2.2 EEG

Regarding the other chosen method, EEG, it is a non-invasive technique and, in comparison with fMRI, it has a better temporal resolution. However, EEG has its limitations. First of all, as it has been mentioned in the introduction it has a poor spatial resolution, which makes source reconstruction challenging. Furthermore, the human brain is covered and protected by a bony skull, and therefore large areas of cortex are unreachable to scalp EEG recording. However, around one-third of the outer convexity of the cerebral cortex is reachable. Also, several tissues (skin, skull, dura, and brain) exist between the source of the generated electrical events and the electrode on the scalp, which might provoke substantial impedance to electrical conduction seen in as a blurring effect at scalp level (Nunez et al., 1994; Srinivasan et al., 1996). As a consequence, the recorded activity is distorted at every electrode, as it is a mixture (i.e. a weighted sum) of the different brain sources (Makeig et al., 1996). Hence, weak electrical signals might be undetected, even those from the surface. Indeed, it has been shown that difference potentials measured from the cortical surface have higher voltages than potentials recorded at the surface of the scalp. A recent study suggested that, besides improving the spatial resolution, high-resolution EEG also improves the temporal resolution (Burle et al., 2015). The experiments presented in this thesis employed high-resolution EEG of 64 channel. Still, this system is not the one with the highest resolution, as there are 128ch and 256ch caps. Interestingly, a recent study suggests that the blur detected on the EEG scalp is not due to the low spatial resolution associated with EEG, but is instead a representation of high-frequency oscillations (Zelmann et al., 2014). Generally, as MMN is an electroencephalogical signal, this methodological approach had to be used to perform the third and fourth experiments.

2.2.3 fMRI and EEG

The last limitation is related to the fourth experiment (section II 4), where EEG and fMRI techniques were employed in a non-simultaneous manner. As it is commonly known, combining EEG with fMRI enables to improve both spatial and the temporal resolution. On one hand, the electromagnetic source can be accurately detected, and simultaneously, the fast neural processes and information pathways within the brain can be monitored. This extraordinary improvement cannot be achieved using these modalities in isolation. In Experiment 4 these two techniques were combined in separate sessions. Using such methodological approach, may induce complex additional variables (see Mulert et al., 2004), such as attention, vigilance, familiarity with the experiment and the given task, or experimental environment (sitting comfortable in a quiet EEG lab or lying inside a noisy and narrow scanner). All these variables might produce differences regarding the neuronal activity. Indeed, there is already evidence of how the level of arousal can influence the activation of brain regions (Matsuda et al., 2002). Ideally, in order to enable the comparison between EEG and fMRI sessions, the above referred variables should be controlled. However, the only way to make the results of the two data sets comparable (in a way that differences between the two session is purely based on the physiological and on fundamental properties instead of confounding variables) would be to simultaneously measure both methods. Due to the technical challenges involved in the simultaneous measurement of EEG and fMRI (for a recent review see Jorge et al., 2014), these two techniques are usually combined with data from separate sessions. Several implementations of simultaneous EEG-fMRI have been presented (Jorge et al., 2014). However, separate sessions of EEG and fMRI data acquisition are not susceptible to the specific artifacts common in the simultaneous EEG–fMRI, this constitutes an important advantage of separate when compared with simultaneous acquisitions. Some experimental designs

simply cannot be accomplished in separate sessions, such as resting-state or trial-by-trial fluctuation studies. Also, for more a truthful comparison between the results of the third and fourth experiments it was necessary to maintain similar experimental conditions. Therefore, in this case the use of the measurement of EEG-fMRI in separate sessions was a better option.

Overall, it is important to state that the prediction related phenomena investigated in this thesis (i.e. RS and MMN) have also been found using other methodological approaches and in other species (RS - Desimone, 1996; Gross et al., 1979; Li et al., 1993; Miller and Desimone, 1994; Miller et al., 1991; MMN - Kaliukhovich and Vogels, 2014; Farley et al., 2010; Fishman and Steinschneider, 2012). This suggests that neither the results nor the main conclusion of this thesis are affected by methodological or species related differences.

3 Open questions and future directions

Please note that in this section I will not repeat the points which have already been pointed out in the discussion above.

3.1 Spatial context and prediction related phenomena

Within the framework of this dissertation, predictions were induced in the temporal context. In fact, the studied prediction related phenomena (i.e. RS and vMMN) occur due to the context imposed by time (e.g. repetition probability; for a review connecting repetition probability with temporal expectations see Matthews and Gheorghiu, 2016). However, information about the environmental statistical regularities can also be based on the spatial context. Actually, it has been suggested that predictions are determined by the analysis of contextual information, which includes both temporal and spatial references (Mizumori, 2013). Indeed, visual objects are assumed to be contextually related if they regularly co-occur in a given environment and context. Predictions are generated via the associative activation of representations that are relevant for that same context (for reviews see Bar, 2004, 2009). For example, an image of a towel can be associated with several objects and different spatial contexts, such as in a bathroom or at the beach. Following this example, when the towel is represented the representation of the possible associations is likely to occur. Though, the efficiency to represent these associations varies according to the given context. Therefore, due to predictive processes the automatic activation of the representation of a soap bar when seeing a towel on the bath-tub is more likely than when seeing it on the beach, which would be misleading. These automatic processes are connected with contextual and associative primings.

Some studies investigated the effects of the two types of contextual predictions (temporal and spatial), on the perception of object trajectory (Doherty et al., 2005; Johnston et al., 2017; Rohenkohl and Nobre, 2011). Generally, in these studies, participants had to infer the trajectory of an occluded moving object to make perceptual judgements based on the direction (spatial context) or velocity (temporal context) characteristics of the objects' trajectory (Doherty et al., 2005; Nobre and Rohenkohl, 2014; Rohenkohl and Nobre, 2011). Briefly, the results of these studies suggest that temporal predictions interact with the spatial predictions in order to improve visual perception. Interestingly, Johnston and colleagues (2017) studied trajectory predictions of the facial expression, rigid-body rotations of faces and bodies and location of faces and shapes by measuring MEG and EEG data. Their results reveal that the early/mid latency of visual evoked potentials (around N/M170) is modulated by the violation of implied trajectory for all stimulus categories. In their studies a sequence of 4 images was used to create the contextual trajectory of implied movement.

Generally, the above cited experiments focused either on trajectory of occluded moving visual objects (Doherty et al., 2005; Johnston et al., 2017; Rohenkohl and Nobre, 2011) or on *apriori* learned associations between different visual objects (Bar, 2004, 2009). Interestingly, MMN can also be influenced by the spatial context, as it is sensitive to perceptual categorization of several domains such as color (Athanasopoulos et al., 2010; Clifford et al., 2010; Mo et al., 2011), vertical symmetry (Kecskés-Kovács et al., 2013a), gender (Kecskés-Kovács et al., 2013b) and laterality of human hands (Stefanics and Czigler, 2012). Still, higher level spatial contextual predictions (similar to Bar, 2004, 2009) have not been investigated using oddball paradigms.

Furthermore, it is still unclear how spatial contextual predictions affect the RS

phenomenon. Until now, the studies investigating the effect of predictions on RS have manipulated the repetition probability (i.e. temporal context). However, as it has been mentioned above: what we predict is not only due to probabilities of repetition or alternation is also due to the context of these. Spatial context may allow the generation of higher-order expectations, which might modulate RS differently than temporal context does (implicitly and explicitly). In order to answer this question, I propose the manipulation of spatial context to induce expectations (in a block or cue-based manner). Therefore, it is not yet known whether spatial expectations add up to or interact with RS, similarly to temporal predictions which explicitly add up and implicitly interact with RS. If the experiment design enables the creation of predictions based on the spatial context, then the effects of spatial context on RS can be tested. I have developed an experimental design to investigate this. In the current thesis I will only present the paradigm that enables to test the influence of implicit spatial contextual predications on RS (see Fig. D 3A). First, it is important to note that in order to exclude predictions driven by Prep, the probability of repetition (Rep) and alternation trials (Alt) is equal, i.e. 50%. Also, one trial would include two stimuli (S1 and S2) and the gender of a trial, i.e. a stimulus pair is always the same, i.e. either female or male. Similar to the Summerfield paradigm the manipulation of expectations occurs within a block. In this case there are Female (FB) or Male (MB) blocks, counterbalanced across participants. In FB the appearance of a female face (Rep or Alt with equal probability) is more likely (75%) than male ones (25%) inducing the spatial prediction of female faces. Similarly, in MB male faces appear in 75% of the trials while female faces are presented on 25% of the trials, enabling the creation of the spatial contextual expectation of male faces. To reinforce these spatial expectations, a male or a female bathroom symbol could appear before the start of the block. Hence, there are expected (female/male faces in FB/MB) and surprising (male/female faces in FB/MB)

events. If the spatial expectations are successfully induced there should be smaller BOLD signal for expected trials. Considering that the spatial contextual predictions are successfully created, we reason that the RS phenomena can be affected in 3 different ways (Fig. D 3B): 1. RS depends on spatial implicit expectations in a similar way to the Prep (xxxx), then there should be an interaction between trial and block types in a way that expected trials have a bigger a bigger repetition suppression index (RSI, i.e. difference between alternation and repetition trials) than surprising trials. 2. RS is not modulated by implicit spatial contextual expectations, then there should be no statistical difference between the RSI of surprising and expected trials; 3. The magnitude of RS negatively correlated with the probability of stimulus features (Sawamura et al., 2006). In this case the surprising trials should show an enhanced response for alternation trials and not for repeation trials.

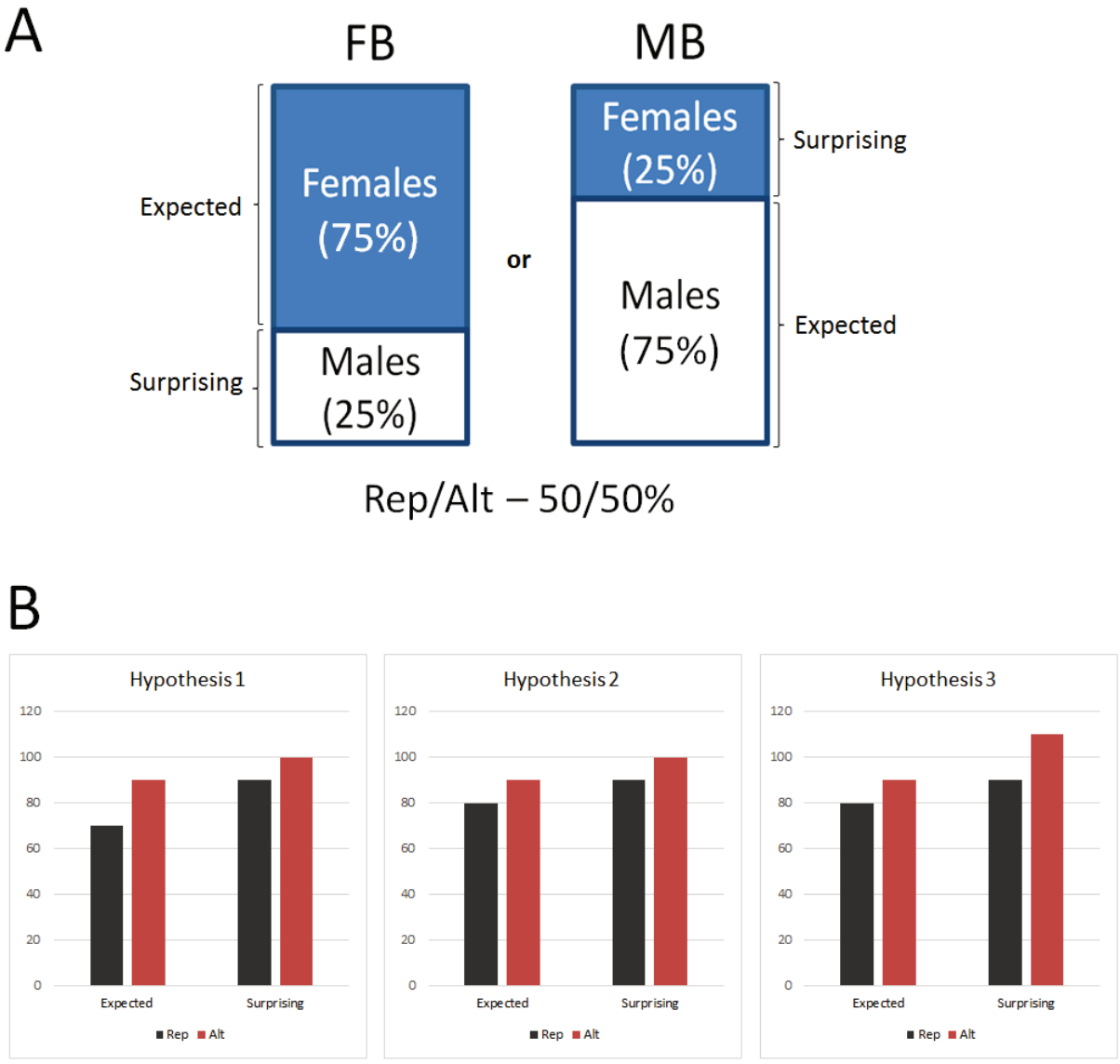

Figure D 3 – A. Proposed paradigm to induce spatial predictions with gender. B. Illustration of the possible hypotheses regarding RS and spatial expectation modulations of the neural responses.

3.2 The role of expertise

Furthermore, the role of expertise in prediction related phenomena is still not clear. Prior studies showed that implicit and explicit expectations are modulated by stimulus expertise (Egner et al., 2010; Grotheer & Kovács, 2014). The expertise hypothesis would suggest stronger prediction effects for familiar / famous stimulus for both prediction related phenomena (i.e. RS and MMN). However, so far, no study has revealed any differences between the electrophysiologically measured MMN induced with stimuli of high and low expertise. Experiment 3 and 4 show similarity of MMN effects between categories that have high and low expertise (i.e. real and false characters). Furthermore, in experiment 3, we found significant vMMN for each of the 4 stimulus categories and the neural mechanisms behind this phenomenon were found to be category dependent but not as hypothesized on the basis of the expertise hypothesis: vMMN of faces and chairs was driven by RS; whereas vMMN of real and false characters was mainly due to surprise-related changes. Still, experiment 4 shows a correlation between the MMN and fMRIa for real characters, only, suggesting that expertise also modulates the MMN responses. Therefore, further experiments are necessary to clarify the role of expertise in prediction related phenomena, specifically on MMN. Clearer evidence for the expertise hypothesis can be achieved by training subjects intensively for previously unfamiliar visual objects (or stimulus from other domain, e.g. auditory) and comparing the expectation effects before and after the training period. The expertise hypothesis would be confirmed if an expectation effect can be detected after but not prior to the training session.

3.3 Unpredictable events

In Experiment 2, there is an unpredictable condition, as in this case repetition and alternation of S2 had the same probability. Predictive theories only describe situations which afford predictability and do not say anything about how the brain deals with completely random inputs. It is known that random events do not enable direct predictive processing, and there is empirical evidence which suggests that the brain might employ similar predictive strategies in an attempt to extract a pattern within the random input (Schellekens et al., 2016; Schubotz and Cramon, 2004; Schubotz and von Cramon, 2002). However, these studies only investigated target motion. In order to understand the predictive strategies used to process unpredicted events it is necessary to adapt the paradigms used in the above cited studies to more complex stimulus. As the prior studies used sequences of trials with a moving target, it is not clear whether these predictive strategies employed to process random inputs depend on memory. From that, several questions arise: 1. Is knowledge about past events (i.e. short-term memory) necessary to create 'prior beliefs' about an upcoming random stimulus? 2. Is there an interference between beliefs and predictions? 3. Can reward modulate the strength of 'prior beliefs' related to random inputs or the intensity of the associated predictive error? 4. Do predictive processes of neutral events depend on stimulus expertise as temporal predictions do? Question 1 has to do with the idea that predictions, i.e. 'prior beliefs' are created according to the conditional probability density function, reflecting the relative probability of the occurrence of a specific event given the available information. However, it is known that the relative probability for the occurrence of random events does not depend on the prior occurrences. For example, when you flip a coin you know the probability of getting heads and tails is the same. Similarly, if you flip a coin nineteen times and it comes up tails each time, the

next toss is not more likely to be a head because the odds are the same (50%). However, the predictive strategies (based on experience) employed to infer random events change when there is access to prior occurrences (19th coin flips) than when there is not (1st coin flip), because we actually expect that the 20th coin flip would be head. The question is if the neuronal processes are the same for these two situations, i.e. if these depend on memory access or not. In any case, when tossing a coin you have to create a belief about the outcome, in other words you have to bet, which leads us to the second question: what distinguishes beliefs from predictions? In fact, most of the literature within the predictive coding framework refers to beliefs and predictions in the same manner (for some examples of recent reports see Kuperberg and Jaeger, 2016). Therefore, one can speculate that if there is a belief about an upcoming stimulus, prediction related processes should also occur, even when the belief is not based on prior events. Still, empirical evidence is required to make such conclusions. The third question has to do with the involvement of rewards when processing neutral events. Random inputs can be associated with rewards, speacially in gambling tasks (e.g. roulette). Indeed, some studies have investigated the error in reward prediction (i.e. the difference between reward occurrence and reward prediction; Hollerman and Schultz, 1998; Schultz, 2016). Briefly, electrophysiological investigations have identified neurons that signal the reward related information, dopamine neurons. However, these studies modulate predictions with the probability of reward, creating more complex and subjective expectations, as those directly depend on each subject. Also, reward-predictions have been mostly studied on animals, such as monkeys, rats and mice. Hence, it would be interesting to know how reward modulates temporal and spatial predictions as well as its involvement on neutral events. The fourth question is related to expertise. As it has been mentioned above, the role of expertise in predictions is not yet well understood, therefore it would be important to test whether predictions

of random events show a similar modulation of expertise than the temporally induce ones. To answer this question it would be necessary to test the beliefs of random stimulus categories with high and low expertise.

3.4 Default predictions and its updating processes

Another open question is related to the processes of updating predictions. Predictive theories argue that prediction updates occur repeatedly, and beliefs are gradually refined until the sensory system settles on the most likely interpretation of the inputs. Following this line of thought, one can reason that if the statistical regularities of an environment are against our "default" predictions (i.e. learned based on experience), the strength of those predictions would be continuously diminished, due to constant updated. However, Pajani and colleagues (2017) revealed that the default prediction of stimulus repetition could not be affected by expectations. Still, this conclusion is based on the fact that repetition trials show similar neuronal activation when presented in alternation blocks (in which more alternating trials than repetition trials) than when presented in predictive alternation blocks (in which alternation is more likely and the pairs of alternating stimulus have been learned, there are therefore temporal and spatial contextual predictions in these blocks). It is important to point that the BOLD signal seems to be smaller for repeated trials when these appear in repetition blocks (i.e. where S2 is more likely a repetition of S1 than its alternation). Taking this into account, repetition seems to be indeed modulated by expectations, namely temporal predictions. Still, the introduction of spatial contextual predictions in the alternating blocks did not affect the repeated trial responses, hence the authors state that RS is not suppressible, which in my point of view is not accurate. First of all because in fact RS is modulated by Prep (Summerfield et al., 2008; Grotheer & Kovács, 2014a; Kovács et al., 2012; 2013; Larsson & Smith, 2012). Secondly, the results found in this study can be due to an interaction between our default and experimental predictions. In a way that, in fact, repetition is always expected as it is the default expectation and, therefore, even with the alternating trials being spatially

and temporally expected, default predictions maintain and are stronger than the experimentally induced predictions. Which brings the question: how much time is necessary to update the default predictions? Training studies would be necessary to answer this question. Further, the results of Pajani (2017) and prior studies (Summerfield et al., 2008; Grotheer & Kovács, 2014a; Kovács et al., 2012; 2013; Larsson & Smith, 2012) suggest that repetition related phenomena cannot be enhanced (via surprise), but instead it can be further suppressed (via implicit expectation). Two experiments (1 and 2) of current thesis revealed no differences between expected and unexpected repeated trials. However, it is not yet known whether repetition is suppressible through general implicit predictions (that do not depend on Prep) or by implicit expectations that directly depend on Prep. To clarify this question, it is necessary to employ spatial expectations (see Fig. D 3 xxx).

3.5 Consciousness and predictions

Additionally, the topic of consciousness in terms of predictions has only begun to be explored. In the framework of the current thesis, cue-based predictions are conscious, as participants are aware of them, however the predictions induced in MMN studies are implicit and, therefore, unconscious. Also, the implicit predictions induced by the Prep modulation are unconscious processes as the participants were not aware of the different Prep in the two condition blocks (Summerfield et al., 2008; Grotheer & Kovács, 2014a; Kovács et al., 2012; 2013). A considerable amount of the predictions we create in our daily life are unconscious, implicit predictions, as those are based on experience and not on cues. For example, you may infer that your colleague is vegetarian if every time you eat together he does not eat meat (probability-based, implicit prediction), whereas you have the knowledge your colleague is going to start a temporary vegetarian diet if he shares that information with you (cue-based, explicit prediction). In the first case, you will need to witness your colleague having lunch for a whileto create those predictions, while with cue-based expectations the belief that your colleague is on a diet is created right after receiving the information and is activated each time you see the cue (seeing him eat vegetables). Similarly, implicit learning, which is also an unconscious process, can become conscious when proper attention is directed towards the contents (Cleeremans and Jimenez, 2002). It is clear that the consciousness level of these two prediction types is different, but it is not yet clear how long does it take us to gain consciousness of our implicit predictions. Will the effects of implicit expectations be different if participants start to be aware of them? However, it is not clear yet how to best separate conscious and unconscious effects on predictions, and how to best think about the state of “cognitive unconsciousness” (Destrebecqz and Cleeremans, 2001; Hama and Leow, 2010).

Overall, all these open questions should be answered in order to improve the existing predictive theories and better understand the prediction related phenomena.

IV Conclusion

The current dissertation clearly shows that two prediction related phenomena (i.e. fMRIa and vMMN) are correlated (Experiment 4). We are the first to test the correlation of such phenomena in category-selective regions for the visual modality and elaborate the necessity to understand the relationship of different prediction related phenomena. In addition, in the current dissertation, we emphazise the role of surprise in both RS (Experiment 2) and vMMN (Experiment 3). Although the neuronal foundation of predictions on this surprise mechanism is unclear, our data indicates that surprise enhancement underlies predictive processes for faces (Experiment 2) and characters (Experiment 3). Further, we could show that cue-based, explicit expectations do not depend on the length of the ISI period between target and cue. Overall, the present dissertation suggests the unification of RS and MMN whitin the predictive coding framework. In this model, RS is described the default prediction, as it is a local and "low-level" effect, while (v)MMN can be due to both low-level and high-level predictions.

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Catarina Pereira Amado (Jena, 12.06.17)

The contributions of the authors

The four studies of this dissertation were part of a project sponsored by the German Research Foundation (KO 3918/1-2;2-1). Before we acquired data, I became familiar with the MRI scanner and EEG, as well as the ethical guidelines. The original idea for Experiment 1 is from Prof Dr. Gyula Kovács. The script was created by Mareike Grotheer and Nadine Wanke. The stimuli belong to a stimulus set that already existed in the workgroup. The data was acquired by Nadine Wanke with my help and me and Nadine Wanke analysed the data. Afterwards, the results were interpreted by me with the hep of Prof. Dr. Kovács. Subsequenty, I did a literature research and created a manuscript, which Prod. Dr. Kovács has discussed and revised with me. The idea of the second study came from Prof. Dr. Kovács and Mareike Grotheer and was worked out jointly with me. The script was created by me, Mareike Grotheer and Petra Hermann. The stimuli belong to a stimulus set that already existed in the workgroup. Afterwards, I collected the data with the help of Petra Hermann and Petra Kovács. The data was analysed by me. Subsequently, I did a literature research and wrote the manuscript, which Prof. Dr. Kovács has discussed and revised with me. Also, Prof. Dr. Vidnyánszky and Petra Hermann have read the manuscript and made suggestions for improvement. The original idea of the third study came from me and Prof. Dr. Kovács. The stimuli belong to a stimulus set that already existed in the workgroup. Afterwards, I programmed the experiment and acquired the data. All the data was analysed by me and interpreted with the help of Prof. Dr. Kovács. Then, I did a literature research and created a manuscript, which Prof. Dr. Kovács has discussed and revised with me. The original idea of the fourth study came from Prof. Dr. Kovács and was worked out by both of us. Polina Stoyanova created the stimuli. I programmed the experiment and acquired the data with the help of Polina Stoyanova. Afterwards, I and Polina

Stoyanova analysed the data. Finally, I did a literature research and wrote the manuscript, which Prof. Dr. Kovács discussed and revised with me.

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Sworn Declaration

I hereby confirm that I am familiar with the current Course of Examination for doctoral candidates of the Faculty of Social and Behavioral Sciences.

Furthermore, I confirm that I have prepared the dissertation myself without having accepted any text sections of a third or my own examination work without identifying it as such. Also, I've specified all the tools, personal notifications, and sources used in my work. The help of a doctoral student was not used. In the selection and evaluation of the material as well as the production of the manuscripts, I was supported by the co-authors (free of charge), as stated in the section bellow: 'The contributions of the authors'. Third parties have not received any indirect or direct monetary benefits from me for work related to the content of the presented dissertation.

This dissertation has not yet been submitted as an examination paper for a state or other academic examinations. Furthermore, no similar, essentially similar, or other treatise was submitted to another university or faculty as a dissertation.

Jena, 12.06.17

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